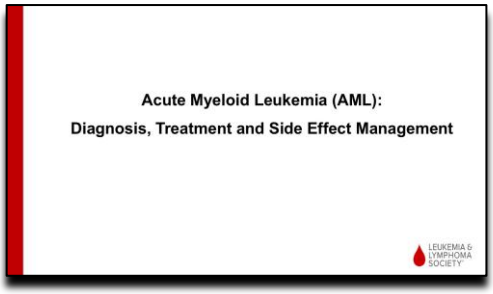
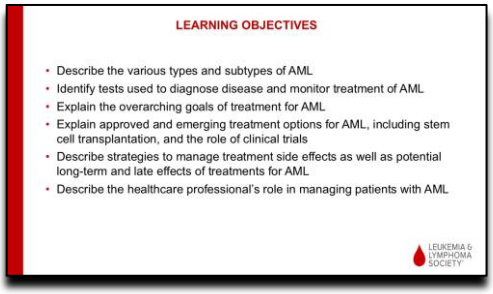


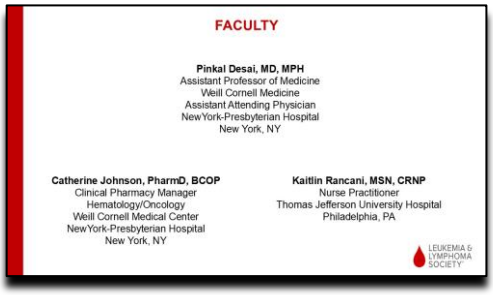
Slide 1: Acute Myeloid Leukemia (AML): Diagnosis, Treatment and Side Effect Management

Lauren Berger, MPH: Hello everyone. On behalf of The Leukemia & Lymphoma Society & Walgreens, thank you for sharing your time with us for this continuing education program on Acute Myeloid Leukemia**:** Diagnosis, Treatment, and Side Effect Management.



Slide 2: Learning Objectives

The learning objectives for this program are listed on this slide.



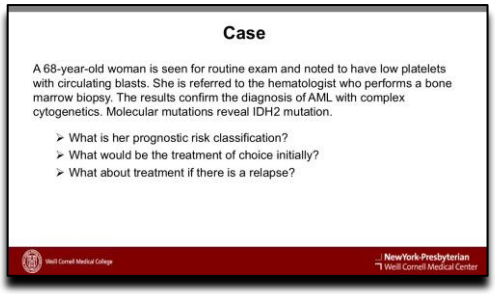
Slide 3: Faculty Slide

We're fortunate to have as our presenters, Dr. Pinkal Desai, a leading expert in AML, Dr. Catherine Johnson, a clinical pharmacist, and Ms. Kaitlin Rancani, a Nurse Practitioner. We appreciate their dedication and their commitment to caring for patients living with blood cancer.

Dr. Desai is Assistant Professor of Medicine, Weill Cornell Medicine and Assistant Attending Physician, at New York Presbyterian Hospital, in New York, NY. Dr. Johnson is Clinical Pharmacy Manager, Hematology/Oncology at Weill Cornell Medical Center, NY Presbyterian Hospital, in New York, NY. Ms. Rancani is Nurse Practitioner at Thomas Jefferson University Hospital, in Philadelphia, Pennsylvania.

Dr. Desai, Dr. Johnson, and Nurse Practitioner Rancani, I am now privileged to turn the program over to You

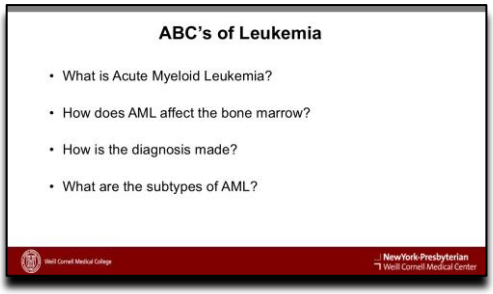
Pinkal Desai, MD, MPH: Hello again. It is my pleasure to talk about acute myeloid leukemia again today with Catherine Johnson.



Slide 4: Case

We are going to begin with a case. Here's a 68-year-old woman who was seen on a routine exam with low platelets and blasts, referred to a bone marrow biopsy, and diagnosis was confirmed for AML with complex cytogenetics, which is defined as more than three cytogenetic abnormalities. Molecular mutations revealed an IDH2 mutation.

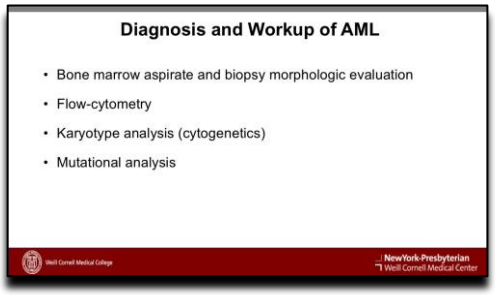
So, some of the questions we always think about when we see patients with AML, what is the prognostic classification? What would be the treatment of choice initially? How do we go about getting into remission, keeping patients in remission? And then if the patient relapses, how do we treat the relapse?



Slide 5: ABC's of Leukemia

So, let's go over what is leukemia first. AML it's a cancer of the bone marrow, as we know. The diagnosis is made generally with the bone marrow biopsy, but it can also be made on peripheral blood. The definition is more than 20% blasts, either in the bone marrow or in the peripheral blood.

There are many subtypes of AML, and there was an old morphologic classification of AML that we no longer use. Nowadays AML is classified based on cytogenetic risk and molecular risk; and also, there are several classifications that we use to not only understand different biological subgroups, but it was also to understand what or how these patients are predicted to do once they are in remission.

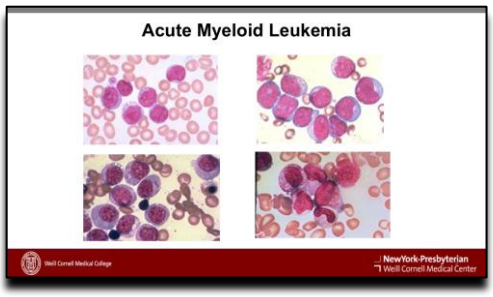


Slide 6: Diagnosis and Workup of AML

The standard of diagnosis, as I said, was from a biopsy and morphologic evaluation. We do a flow cytometry analysis that gives us, to some extent, some subtype information, particularly the differentiation between APL or acute promyelocytic leukemia and non-APL. And to make this simple, we are not discussing APL in this presentation because it's a lot; and it's very, very specific and different. I'm going to focus on AML that is not APL.

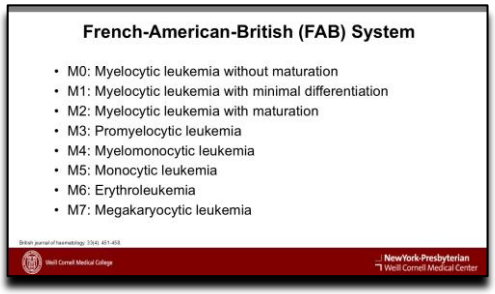
We always do cytogenetics. This is central to understanding what treatment we need to give and how the patients are predicted to do. And so, our mutational analysis, because again, there are targeted agents that can work against certain mutations; and even in

those that don't have targetable mutations, it helps us understand, again, the prediction of how patients are going to do in the future and the decisions on transplant versus not.



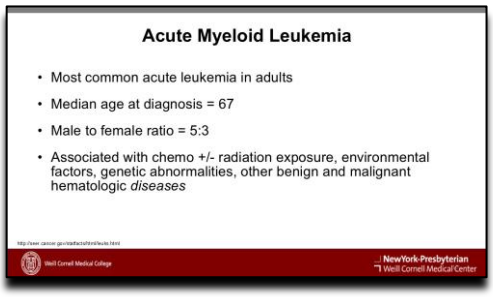
Slide 7: Acute Myeloid Leukemia

This is how an AML blast may look on blood or bone marrow, usually large cells with most of the cells being occupied by these nucleus with some nucleolus right here in the middle. This, obviously, is, is a pathologic diagnosis. Morphology is not, these days, sufficient. You really do need to have flow cytometric evidence as well.



Slide 8: French-American-British (FAB) System

This is the old classification I was talking about based on morphology again. None of this is relevant in these days other than calling out just the M3, which is the promyelocytic leukemia; and that is the only morphologic classification that is relevant and treated very differently. Else all is kind of, in terms of treatment and prognostication, not that relevant because we have a better way of understanding how patients do based on cytogenetics.

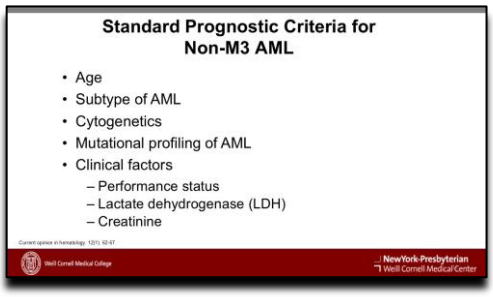


Slide 9: Acute Myeloid Leukemia

AML is the most common leukemia in adults. Median age at diagnosis is 67. It is more common in males compared to females. It can occur de novo, which is basically with no previous exposure to any chemotherapy or other cancer. That's considered de novo AML, and it can also occur secondary to previous insults to the bone marrow, either in the form of chemotherapy or previous hematologic malignancies; and that is considered secondary or therapy-related AML. AML is generally not genetically inherited. The most commonly, this occurs as a random mistake, an error. Approximately 5% to 8% of AML has a genetic component, which is inherited. We always like to ask for family history to understand if we have to work up familial predisposition to AML. But for the most part, it is occurring as a random error.

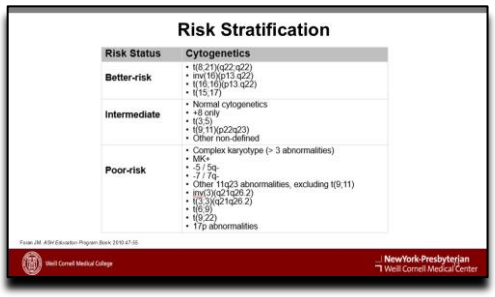
Why are these de novo versus secondary and therapy-related AML classification important? Because therapy-related AML is generally associated with worse prognosis and also has higher cytogenetic abnormalities that are considered bad risk. So, it's good to know this because we're already anticipating when we are seeing the patient that we are going to find a certain phenotype and molecular subtype and cytogenetic subtype for

that particular AML. We were preparing ourselves for different treatments based on that information.



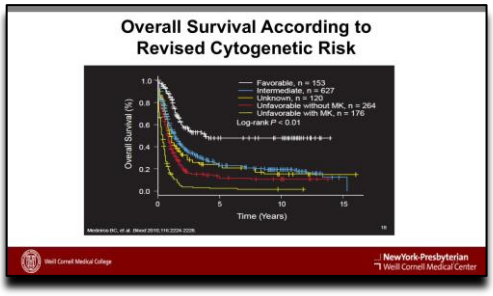
Slide 10: Standard Prognostic Criteria for Non-M3 AML

So, when we look at the patient and we diagnose AML, again, this is non-M3 AML. We look at all of the other characteristics which we talked about, but in addition to that, clinical factors are also important. How does a patient look that is designed as performance status, which we care about people who are having a good performance status, are more likely to tolerate intensive chemotherapies, so that is central to our assessment of, early sort of intensive therapy versus lower intensive therapy. And also organ function which is creatine and also the heart function. We always do an echo at baseline. All of this goes into understanding what is the best treatment suited for the patient.



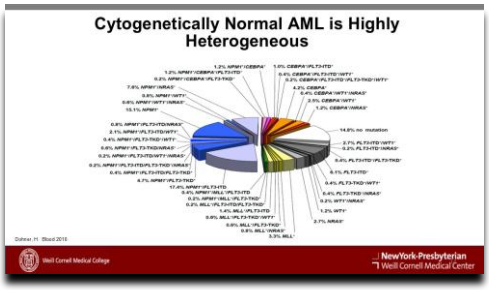
Slide 11: Risk Stratification

And here is the risk stratification for, just based on sort of cytogenetics. The good risk is 8;21 core-binding factor and 15;17 translocation. 15;17 is the APL that we talked about. Poor risk is anybody who has complex karyotype and certain cytogenetic abnormalities, as listed over here, including TP53a; and if you're not better risk or poor risk, it's basically intermediate risk. And again, this, we will talk where this information goes in the decision-making.



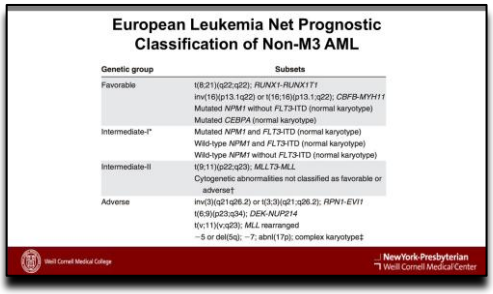
Slide 12: Overall Survival According to Revised Cytogenetic Risk

Survival is important in, and it's something we are always striving for in our patients with leukemia. As you see on this graph, there is a big, big difference in somebody who is favorable versus somebody who is not, where the long-term cure rates beyond five years are really dismal in people who are poor risk. While in good-risk leukemia, depending on the subtypes, we're able to cure more than 50% to 60% of patients with favorable risk.



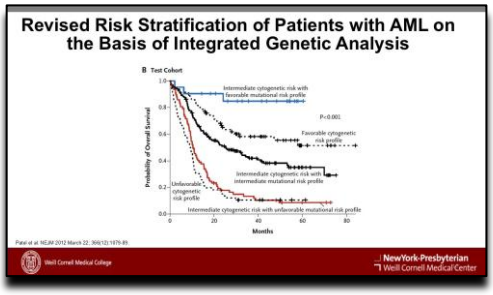
Slide 13: Cytogenetically Normal AML is Highly Heterogeneous

Even when we think about cytogenetically normal AML, which falls into the intermediate-risk category of cytogenetics, this is a very complicated group because based on all the mutations that we send and they come back, patients are very heterogeneous. As you can see, there are, many subgroups of this disease; and we have to look at all of these mutations in order to understand how they will do in the future.



Slide 14: European Leukemia Net Prognostic Classification of Non-M3 AML

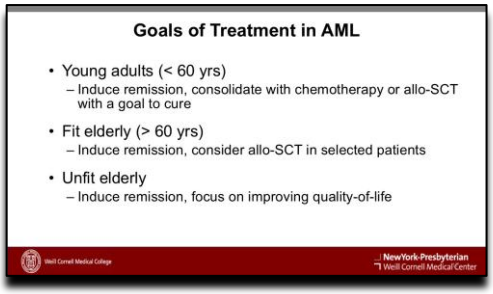
So, why do we have a combined classification? Because, in, particularly in people who have normal cytogenetics based on the mutations, you can subdivide AML into different categories when you add the mutational subgroups to it based on FLT3, NPM1, some of the other mutations. All of this goes into dividing what is considered favorable, intermediate, and adverse risk. And we will talk about again in the in the slides coming up what, how we decide this further treatment.



Slide 15: Revised Risk Stratification of Patients with AML on the Basis of Integrated Genetic Analysis

So, when you think about this revised classification, based on the combined cytogenetics as well as mutational profile, we will find that people who are favorable, again, have a very good survival risk, 80% long-term survival. Those who have a poor cytogenetic and mutational subgroup have an inferior survival. And then here where you divide people into sort of a favorable cytogenetic risk profile and intermediate cytogenetic risk with intermediate mutational risk profile, you're really dividing a very wide survival curves; and this is important because you don't want to transplant somebody who is going to do very well. And you definitely want to transplant somebody who is going to do poorly.

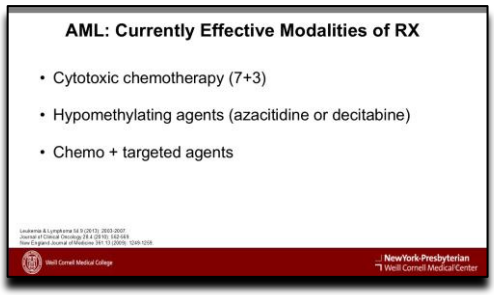
Again, the subclassification is a lot; and that's not the intent of this thing. But to understand why these mutations are actually important.



Slide 16: Goals of Treatment in AML

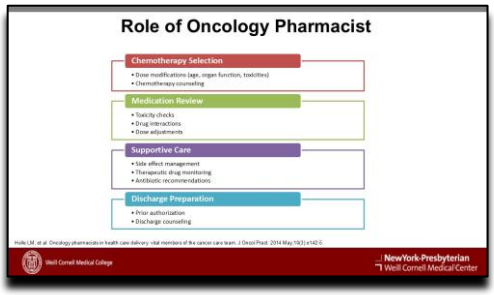
So, what are the goals of AML treatment? In the young adults, and we generally consider that less than 60 years, the goal is to induce remission. And then we do consolidation. Getting into remission does not mean that we cured these people. There's always some leukemia that's left behind; and you have to consolidate these patients with either chemotherapy or allogeneic stem cell transplant with the goal to cure.

In patients who are fit and elderly, so over 60 but fit and can handle treatment, both intensive and not intensive, again, the goal is inducing remission and considering allogeneic stem cell transplant in selected patients who can actually handle stem cell transplant. In unfit elderly, the goal is to induce remission and keep them in remission for as long as we can. We generally do not cure unfit, elderly patients; but we can put them into remission for a while. And the focus is on improving quality of life and making them transfusion independent.



Slide 17: AML: Currently Effective Modalities of RX

So, what are the currently effective modalities of treatment? There is cytotoxic chemotherapy. More commonly, we use a combination of cytarabine and daunorubicin (Vyxeos®). We call them 7+3, hypomethylating agents and also combinations of chemotherapy and targeted agents. We're going to go over some of these regimens in the future, so this is a little early.



Slide 18: Role of Oncology Pharmacist

So, obviously, with all of this, we work hand in hand very much with our oncology pharmacist. We probably will not function at all without the role of our pharmacist, and Catherine Johnson will talk about that.

Catherine Johnson, PharmD, BCOP: So thank you, Dr. Desai, for that introduction. I want to express my gratitude towards having such a wonderful team that's very welcoming and appreciative of pharmacists. And the oncology pharmacist is just one of the many important members of the care team when it comes to treating an AML patient.

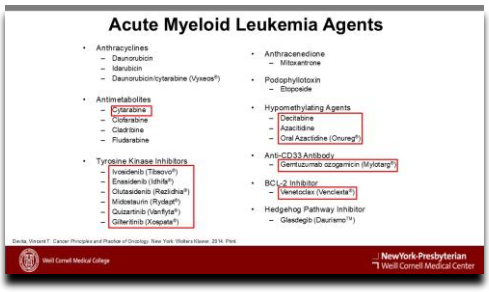
As pharmacists, we work alongside the physicians as well as other members to make sure that patients receive appropriate medications, not only in a safe but also effective way. Patients may encounter pharmacists in a lot of different settings, whether that's the hospital, in the clinic, or even in the community setting.

The oncology pharmacist is truly helpful when it comes to individualizing and selecting the right chemotherapy for patients; and this can be based on a patient's age, organ function, underlying comorbidities, allergies, drug interactions with medications they're already on, and accounting for any history or previous treatments. Pharmacists are also heavily involved in chemotherapy counseling and in providing educational material to not only patients but also caregivers.

After starting treatment, the pharmacist is responsible for frequently and thoroughly reviewing the medications that patients are on to see if anything should be added, removed, or adjusted. We really want to optimize the patient's care as best as possible, and we do that also by conducting toxicity checks and lab checks to see how well they're tolerating and see if we need to make adjustments.

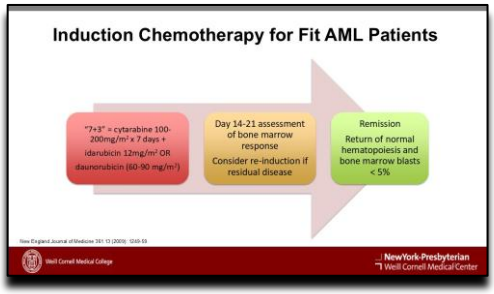
Pharmacists are not only optimizing the chemotherapy but also any supportive care connected to the treatment of a newly diagnosed AML patient because when you think about it, these patients who are receiving induction chemotherapy for the first time, they are at risk for different infections and different complications. So, we really help with identifying the right preventative anti-infectives, adding medications to prevent nausea/vomiting, minimizing cancer-associated pain, and any other side effects that may come a patient's way.

Pharmacists also have a key role in monitoring drug levels of certain medications to make sure that they're getting the safe amount, and pharmacists can also tailor antibiotic regimens appropriately for patients. As patients are ready to be discharged, as you can imagine, when they leave the hospital they are often started on more medications than they started with. So, as pharmacists, it is our responsibility to ensure that they have a smooth transition to home. Our responsibilities towards the end include assisting the medical team in securing prior authorizations, adjusting any barriers to adherence, reviewing discharge medication lists, and providing discharge counseling so it's very clear what patients have to take at home. And we will continue to support them in the outpatient setting as well.



Slide 19: Acute Myeloid Leukemia Agents

So as Dr. Desai mentioned, there are so many different regimens and, in the acute myeloid leukemia space, most of which include cytotoxic chemotherapies. But oral targeted therapies have also expanded and transformed the treatment landscape of AML. The drug classes here include the most common medications used for AML, whether it's used in the upfront setting or relapsed/refractory setting. We will touch upon the ones boxed in red more in-depth in the upcoming slides.



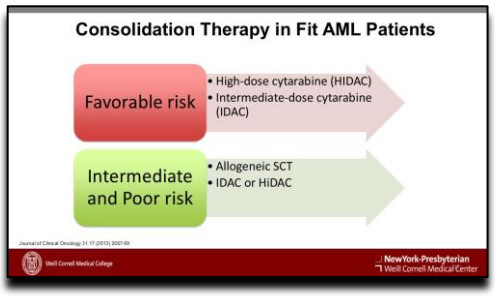
Slide 20: Induction Chemotherapy for Fit AML Patients

Dr. Desai: So, we're going to talk about initially, fit patients and then go through what regimens are available for upfront treatment for all the fit patients, whether molecularly targeted chemotherapy combinations, all of that. So, in general, if you think about like the backbone of intensive chemotherapy, and I'm using 7+3 as an example, but there are other backbones also available. 7+3 happens to be the more common backbone that is used in the US. The 7+3 is given, which is combination of cytarabine given for seven days as a continuous infusion and idarubicin (Idamycin PFS®) or daunorubicin (Vyxeos®) which is given for the 3 days, hence 7+3.

Once the chemotherapy part is given, we usually do a bone marrow assessment around day 14 through 21. And the intent of this assessment is to make sure that we have eliminated most of the leukemia and the bone marrow should appear empty or ablated, which is generally traditionally defined as a cellularity less than 5% and blasts less than 5% to 10%. If we reach there, then we don't do anything and allow the patient to recover and the bone marrow to recover.

But, if you find at this stage there is still enough leukemia left behind that we almost anticipate that this is going to come back with full blown disease, then we consider a reinduction if the patient's clinical status is okay and enough to get another induction. And usually, we give that as a repeat of 7+3, or we give a 5+2 or sometimes a change, depending on how much kill we have achieved around that time. Once we do this, either we don't give chemo or do reinduction, then again, we wait for the bone marrow to recover. As I said at that 30-day mark on an average, usually patients will start recovering their blood counts and they make some kind of clinical blood count recovery. We do another marrow. This is considered our remission check marrow. Here we want the return of normal hematopoiesis, and the bone marrow blasts should be less than 5%.

So, this is what is termed the entire thing as induction. This happens in the hospital for patients who are getting intensive chemotherapy because it is not safe to do this outpatient. The chances of neutropenic fevers are very high, and we have to protect them from all kinds of infections and complications from chemotherapy.

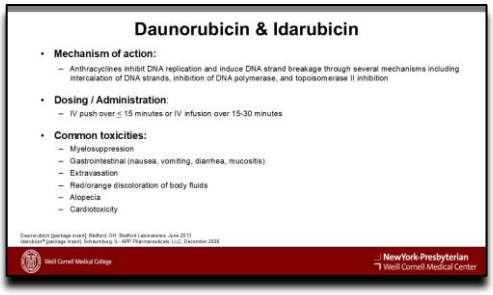


Slide 21: Consolidation Therapy in Fit AML Patients

So, let's say a patient is in remission, then what do you do next? Again, we have mentioned this before that this doesn't mean we cure the patient. There is still some measurable residual disease left in patients. So, here is where all that risk classification that we talked about previously comes into play. So, if somebody is favorable risk, as defined by the ELN risk, then we would give more cycles of consolidation chemotherapy, which is usually in the form of HiDAC or high-dose cytarabine, generally defined as 18 grams per meter squared; and intermediate is somewhat less than that. Twelve is the standard, but again, we sometimes modify the doses, depending on tolerance. The reason we give only chemotherapy here and not an allogeneic stem cell transplant is because their cure rate is higher; and giving a transplant actually puts them at a higher mortality risk. And it's better to give chemotherapy rather than do a stem cell transplant.

But if somebody's intermediate or poor risk, then we generally attempt to do an allogeneic stem cell transplant. There may be institutions that do not transplant intermediate-risk patients; but we tend to always evaluate that because as I said, between all those little subgroups that exist, it's really hard to judge who is the intermediate risk that does or does not need a transplant? So, we try to favor allogeneic transplant if we can.

In case the patient does not want it, is not eligible, there is no donor, or is too sick, then you can go ahead with the same sort of intermediate dose, a consolidation if needed.



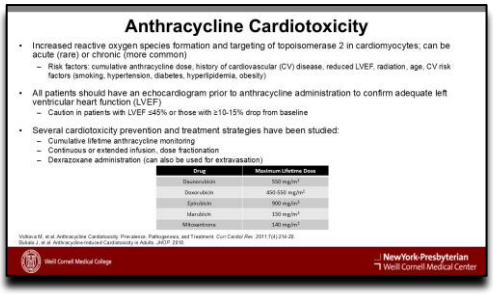
Slide 22: Daunorubicin (DaunoXome®) & Idarubicin (Idamycin PFS®)

So, Catherine's going to talk about the infamous 7+3 at the moment.

Dr. Johnson: Thank you, Dr. Desai. So, when we think of 7+3 induction, typically when we think of what makes a regimen intense is really the anthracycline component. So, in AML, the two most common anthracyclines you'll see us use are daunorubicin (DaunoXome®) and idarubicin (Idamycin PFS®). They're both given intravenously over a short, 15- to 30-minute push or infusion. And they do undergo hepatic metabolism to both active and inactive compounds. So, we just need to take into

consideration patients with underlying liver dysfunction to make sure we're giving them the appropriate dose.

In terms of toxicities, myelosuppression is by far the biggest one to expect. And again, this is why we have to be thoughtful about which patients should be receiving an anthracycline. Patients will probably see worsening of their blood counts before they see eventual normalization. Patients also tend to have nausea and vomiting, for which they will typically receive two premedications prior to anthracycline administration. Extravasation is the term that we typically use when the IV catheter being used to infuse the anthracycline comes out of the blood vessel and causes leakage into the surrounding tissue. And this can cause potential injury and damage. But it's important to note that the risk is higher usually in patients with poor veins or if they're getting a long anthracycline infusion. But in this case, in our AML patients getting 7+3, it's less common because, again, they're only getting it for 15 minutes, max 30 minutes, and there's a nurse at bedside during administration. But it's still something to be aware of. Patients may also notice that their bodily fluids, whether it's urine, sweat or tears, may temporarily change to like a more orange or red tinge in color. And this is completely normal, and this should not cause any panic. This is truly because the medications themselves are red in color, and it's just your way of your body showing that it is being eliminated. And finally, one of the most important toxicities we have to think about is anthracycline-induced cardiotoxicity.



Slide 23: Anthracycline Cardiotoxicity

So, the mechanism of anthracycline-induced cardiotoxicity is multifactorial. But essentially, it boils down to the fact that there is direct injury happening to the cardiomyocytes, and there is increased oxidative stress over time.

Cardiotoxicity can manifest in one of two ways. Acute cardiotoxicity is more secondary to an inflammatory response and presents as palpitations or arrhythmias, but this is generally very rare. Chronic cardiotoxicity, on the other hand, is more common, where patients experience a decrease in ejection fraction over time. So, that relates to how well your heart is pumping. And some patients can experience cardiomyopathy over time.

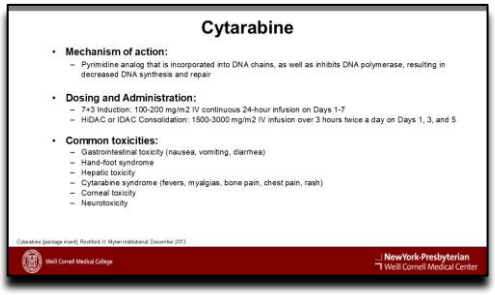
So, prior to initiating chemotherapy, patients should receive a baseline echocardiogram to confirm their ejection fraction; and we'll also assess for any risk factors that might increase their risk of chronic cardiotoxicity, so this can be previous heart disease, age, radiation exposure, smoking, high blood pressure, etc. And if we find that the patient has an ejection fraction below 45% or 50%, or they have a 10% to 15% drop from baseline or, again, they have significant risk factors, they will most likely not receive an anthracycline because the risk outweighs the benefit. One of main risk factors for anthracycline-induced cardiotoxicity is the previous exposure to anthracyclines, which is tracked with each

treatment. The table I have listed here is giving you the cumulative anthracycline doses patients are allowed to have in their lifetime because the closer you are to this number, the higher the incidence of cardiomyopathy.

This is particularly important when you think of patients who have been treated with anthracyclines in the past for another malignancy. So, for example, a newly diagnosed AML patient with a past medical history of breast cancer, probably treated with four cycles of AC has received 240 of the 550 milligrams per meter square acceptable for their lifetime cumulative dose of doxorubicin (Adriamycin®). It's possible that when you repeat the echocardiogram, the ejection fraction could have maybe reduced. But let's say it's still normal. Even if they're eligible, we have to ensure that they still do not exceed the lifetime maximum dose if we were to give them additional anthracycline.

So, there are a few ways to prevent and monitor these cardiotoxicities besides just ejection fraction assessments and lifetime dose tracking. We can extend the duration of the infusion or break up the doses over several days to give a less peak effect and less damage at once.

There's some data about ACE inhibitors or ARBs to have some cardioprotective effect if you have a baseline cardiomyopathy. And dexrazoxane (Totect®), which is typically an antidote used for extravasation, can also be used as a cardio-protectant in patients who have received a certain amount of anthracycline already. Although these strategies aren't commonly used in AML, they are worth noting in case it's necessary.

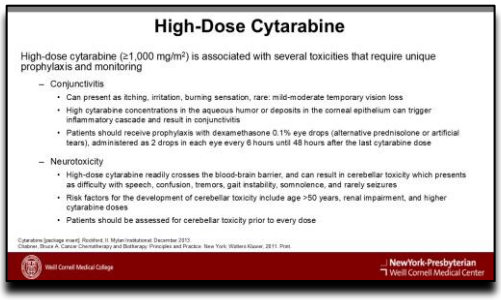


Slide 24: Cytarabine

The other integral part of our 7+3 backbone is cytarabine. The dose and how we administer cytarabine really depends on how you're receiving it. So, when you're receiving 7+3 induction chemotherapy, you're receiving cytarabine at lower doses, continuously over seven days, whereas when you're receiving high-dose cytarabine for consolidation, cytarabine is given at extremely high doses over three hours, twice a day, every other day. Both methods help to overcome any resistance from the enzymes trying to break down the cytarabine itself. It is hepatically metabolized into several active and inactive metabolites, so again, paying attention to their hepatic function is very important.

Although there seems to be like a wide range of toxicities listed here, I want to make sure everyone knows that the dose truly impacts not only the type but the likelihood of what type of side effects a patient might experience. Nausea, vomiting, diarrhea, these can all occur at any dose. But the higher the dose, the higher the chances, which is why we tend to add more preventative medications. Some patients can experience rash or low-grade

fevers or itching on the sole of their feet's or hands. And then corneal toxicity and neurotoxicity are rare and tend to only occur at high doses.



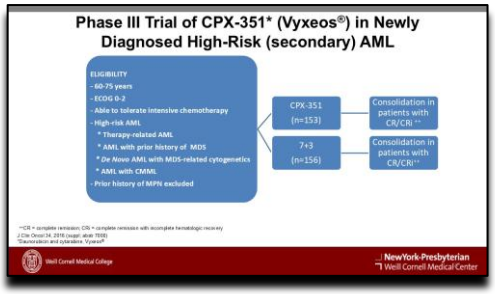
Slide 25: High-Dose Cytarabine

When we refer to toxicities associated with just high-dose cytarabine, this is for doses specifically greater than or equal to 1 gram per meter squared, which again we've talked about is associated with HiDAC or IDAC consolidation. So, when we're administering high-dose cytarabine, there are a few unique preventative measures and monitoring that we require while you're in the hospital. Chemical conjunctivitis or corneal toxicity occurs due high cytarabine concentrations in the aqueous humor or some deposits that can happen in the corneal epithelium. And this ultimately triggers an inflammatory response. For most patients, if this were to occur, it presents as mouth itching, irritation, or sometimes burning sensations. But in rare cases can cause pain or temporary vision loss.

This toxicity is really rare because of two reasons. One, we pick the right dose in patients who are older or have poor kidney function. We ensure we reduce the dose; and this ultimately reduces the risk of the side effect from happening all together. And two, all patients are required to receive some form of preventative eye drops throughout cytarabine treatment and after treatment.

Typically, we give our patients two drops of dexamethasone (Mattapan®) eye drops in each eye every six hours on the days they do receive high-dose cytarabine and two to three days after the last cytarabine dose. The frequent eye drops help to flush the eye, and the steroid component helps decrease any associated inflammation. If there's a drug shortage, which happens a lot, prednisolone (Prelone®) eye drops or artificial tears are acceptable alternatives.

The other key toxicity we can see with high-dose cytarabine is neurotoxicity, and this happens because the chemotherapy itself crosses the blood-brain barrier. Neurotoxicity can present as difficulty with speech, gait, confusions, tremors, somnolence, and in very rare scenarios seizures. Patients, again, who are at higher risk are patients who are above the age of 50, baseline kidney dysfunction, and again experiencing higher doses. Therefore, these patients will likely get an intermediate dose or IDAC for consolidation; and we want to make sure that before each dose of cytarabine, patients are assessed for cerebellar toxicity. So, one of the most common ways is having our nurse ask you to sign the name prior to each dose. And they'll track any slight changes in hand movement or signature patterns because this can signal cerebellar toxicity. In the rare event any of these toxicities occur, we would immediately stop the cytarabine.

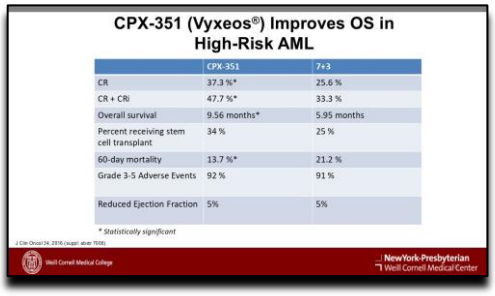


Slide 26: Phase III Trial of CPX-351 (Vyxeos®) in Newly Diagnosed High-Risk (secondary) AML

Dr. Desai: So, I would like to mention here that, obviously, when you give this, there's lots of toxicities. But the induction mortality from 7+3 is actually less than 5%. So, in the hands of a leukemia center where people are watching them, they're inpatient, most patients will survive this but with a lot of, obviously, pulling them through complications of treatment. So that's sort of our backbone of therapy. It is generally what we would use in de novo AML with modifications based on molecular mutations, which we will talk in the future. But what about secondary AML?

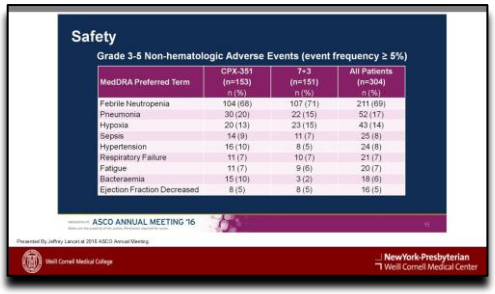
So, CPX-351 (Vyxeos®), also known as, liposomal daunorubicin and cytarabine, is currently approved for high-risk secondary AML. This was based on a Phase III study that enrolled 60 to 75 years of age. However, the drug is approved for everybody with secondary AML. Good performance status. They have to have therapy-related AML or AML with previous MDS or what appears to be de novo AML but has MDS-like cytogenetics, which is basically saying biologically you had something going on for a while before the AML happened.

And patients were randomized to CPX-351 (Vyxeos®), and 7+3, which is the backbone we just talked about. 7+3 was until more recently, the backbone for almost every AML. And now we know there is many, many variations that we do affect, which we'll talk later. Patients then were consolidated with the same regimens, CPX or 7+3 based on randomization. They were allowed to go to transplant. No decisions was changed in terms of post-consolidation therapy.



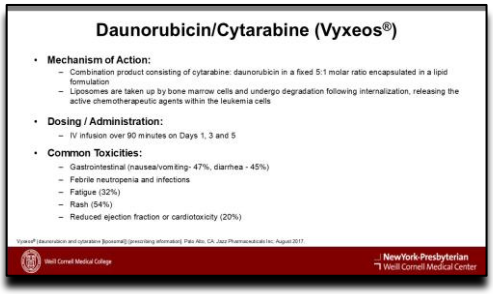
Slide 27: CPX-351 (Vyxeos®) Improves OS in High-Risk AML

And here were the results that led to the approval, the CR + CRi, which is complete remission and rates was about 47.7% in the CPX arm and 33.3% in 7+3 arm. And there was significant improvement in survival. More people went to transplant when they were treated with CPX-351 (Vyxeos®). The 30-day and 60-day mortality was also lower in the CPX-351 (Vyxeos®) arm compared to 7+3 arm.



Slide 28: Safety

And in terms of safety, when we talk about, there was no major sort of things that popped up. Both were sort of equal. As you see, the febrile neutropenia rates were pretty similar in general. So, it was considered safe, and the mortality was actually lower; and that led to the approval of the drug for the secondary AML patients.



Slide 29: Daunorubicin/Cytarabine (Vyxeos®)

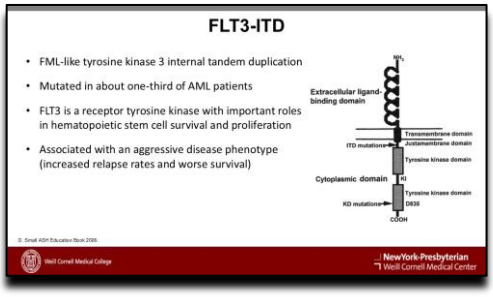
Dr. Johnson: So, liposomal daunorubicin and cytarabine (Vyxeos®) is similar to 7+3 in the sense that it does contain the same backbone agents, daunorubicin and cytarabine (Vyxeos®). But the distinct difference is that liposomal daunorubicin is a combination product with a fixed 5:1 ratio. The liposomal combination is selectively taken up by these bone marrow cells. It undergoes degradation and eventually releases the active chemotherapy agent to the malignant cells themselves.

The thought with the unique mechanism associated with liposomal daunorubicin and cytarabine was that this would prolong the effect of these active chemotherapy agents while also decreasing the incidence and the degree of toxicities described earlier. Liposomal daunorubicin or cytarabine, which again is also noted as CPX-351 (Vyxeos®). It's a 90-minute infusion given on days 1, 3, and 5 of induction. And if you need to give liposomal daunorubicin and cytarabine again, whether it's in the form of reinduction due to residual disease or for post-remission consolidation treatment, the dose and/or the frequency will be different. There is a black box warning to alert prescribers to note the differences between your conventional 7+3 and this liposomal daunorubicin-cytarabine formulation. They are not interchangeable, and they should not be confused with each other.

The toxicities are pretty similar, as Dr. Desai had mentioned earlier, the nausea, vomiting, and diarrhea, rash, and cardiotoxicity are still seen with Vyxeos, so we need to make sure we premedicate and monitor appropriately. In the studies, they did see more prolonged myelosuppression and time for count recovery; so, it's very possible that since these patients will experience neutropenic fevers and infectious complications, they need to be monitored in the hospital while receiving appropriate anti-infective therapies in case they spike a fever.

Dr. Desai: It's an important point to notice here is that in spite of a slightly delayed myeloid recovery, the general toxicity profile was considered safer than the traditional 7+3. And because this is more sort of targeted to the bone marrow, if you may say, the off-target

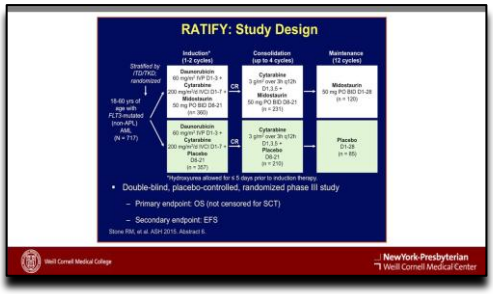
effects are lesser. So, the GI toxicity's actually better with liposomal daunorubicin and cytarabine; and patients don't lose their hair so much, which is again saying, it's not going into like more systemic. And it's mostly released inside the bone marrow.



Slide 30: FLT3-ITD

So, now we're going to talk about all of the mutations that we talked about previously and how they modify. So, we have our first subgroup of secondary AML where the standard is actually now CPX-351 (Vyxeos®) or liposomal daunorubicin and cytarabine. Now, what about the other groups of patients; and what are their standard?

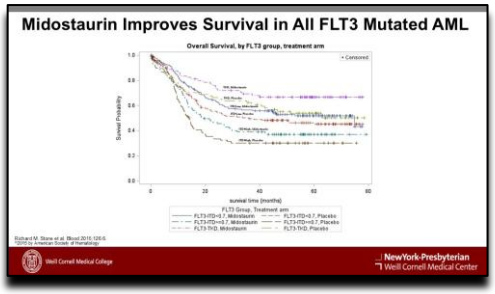
So FLT3-ITD is an important mutation that we see in AML. It's common. It's, one-third of AML patients have it. There are two kinds of mutations, ITD and TKD or tyrosine kinase domain mutations are generally associated with high white cell count. Hence, particularly FLT3-ITD is associated with an aggressive disease phenotype. So, this was prior to what the current therapies are in the past. Before we had better therapies for FLT3-ITD and TKD, this was considered a very, very, very high-risk disease that universally relapsed, even after transplant.



Slide 31: Ratify: Study Design

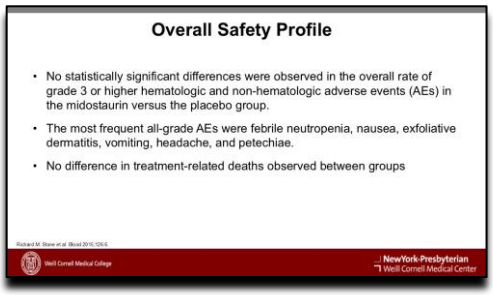
What changed are the age of the FLT3-targeted drugs. The first drug that was approved in this was midostaurin (Rydapt®). This was a large, randomized study. It was the RATIFY study where young patients, 18 to 60, with FLT3-mutated, both TKD and ITD mutations were allowed onto the study. Patients were given as 7+3, which is the, sort of the, the back, the standard arm. And the investigational arm was 7+3 in midostaurin (Rydapt®) given as 50 milligrams twice a day, day 8 through 21. So, it began after 7+3 stopped.

Consolidation was given in a standard fashion. Cytarabine, along with midostaurin (Rydapt®) or placebo based on randomization. And maintenance was also given in the midostaurin (Rydapt®) arm. And in the placebo it was, obviously, placebo, it was about 12 cycles of maintenance that was given. Patients were allowed to go to transplant based on clinical judgment.



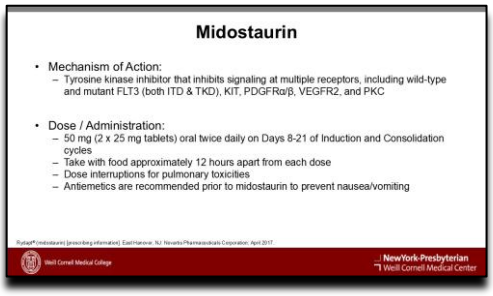
Slide 32: Midostaurin (Rydapt®) Improves Survival in All FLT3 Mutated AML

And the results was improved overall survival in almost all subgroups favoring the midostaurin (Rydapt®) arm. Both FLT3-ITD and TKD responded and had better survival compared to placebo. And in ITD, there used to be an old classification of ITD-low and ITD-high based on how much FLT3 you had in the bone marrow. That is actually almost irrelevant now and out of our classification because patients do so well with the FLT3 mutations that we no longer consider the allele fraction or how much FLT3 you have as prognostic at all. So, the point at that time, this was the case; and it was demonstrated that both the low and the high fractions responded better with midostaurin (Rydapt®).



Slide 33: Overall Safety Profile

Generally, no significant toxicity differences were seen overall; and there was no excess mortality, but we're going to talk a little bit more about the toxicity and drug with,
Catherine.

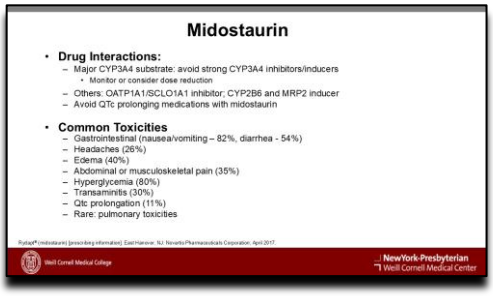


Slide 34: Midostaurin (Rydapt®)

Dr. Johnson: So, the RATIFY trial really led to the approval of midostaurin (Rydapt®) back in April of 2017. And then as Dr. Desai mentioned, it targets both ITD and TKD mutations; so, it was really revolutionary at that time.

Midostaurin (Rydapt®) does not only inhibit FLT3 receptors but also other receptors in our body such as KIT, PDGFR, VEGF, and PKC family. The typical dose is 50 milligrams twice daily for 14 days during induction and consolidation after the IV chemotherapy component is complete. It's important that we take these tablets with food approximately 12 hours apart, and this helps not only with absorption, but it also helps to minimize the side effects that I'm going to talk about.

It does undergo hepatic metabolism via CYP3A4 to active metabolites, and these metabolites also have a very long and variable half-life. So, we have to think about drug interactions not only while they're on midostaurin (Rydapt®) but shortly thereafter. It's also recommended to take an antiemetic about 30 to 60 minutes prior to midostaurin (Rydapt®) to prevent nausea and vomiting.



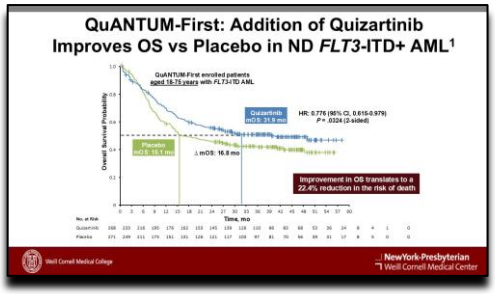
Slide 35: Midostaurin (Rydapt®)

So, with any oral chemotherapy agent, as you can imagine as pharmacists, it's important to review for any drug or food interactions. Since midostaurin (Rydapt®) is a major CYP3A4 substrate, we try to avoid CYP3A4 inhibitors, specifically strong ones, as well as inducers when possible. But, unfortunately, there are going to be situations where some interacting medications cannot always be avoided.

So, one example of this is for a newly diagnosed AML patient undergoing intense treatment, whether it's 7+3 or Vyxeos. They're going to be at high risk for invasive fungal infections while their neutrophil count is so low. So, we will have them routinely on some sort of fungal prophylaxis; and the two most common agents you should see are posaconazole (Noxafil®) or voriconazole (Vfend®). Both of these drugs, however, are strong CYP3A4 inhibitors, and they are necessary when it comes to the AML supportive care bucket. Therefore, like when you're thinking of this complex scenario, we need to have an interdisciplinary discussion and tailor our approach to the patient to account for these higher concentrations of midostaurin (Rydapt®) that we anticipate and trying to minimize the toxicities from that as well.

So, one of the strategies to consider is an alternative antifungal that maybe has less inhibitory effects. So, one example could be isavuconazole (Cresemba®). Another option is to consider reducing the dose of midostaurin (Rydapt®), and this is maybe a great option for our, some of our elderly patients who may be more sensitive to side effects from the higher concentrations. And lastly, some of our providers are okay with just monitoring them with both drugs on board because they're here anyways in the hospital; and so, we can monitor for any of the side effects. We also try to monitor the QTc interval, not only at baseline but frequently throughout treatment. And whenever possible, we try to minimize any drugs that are known to elevate the QTc as well.

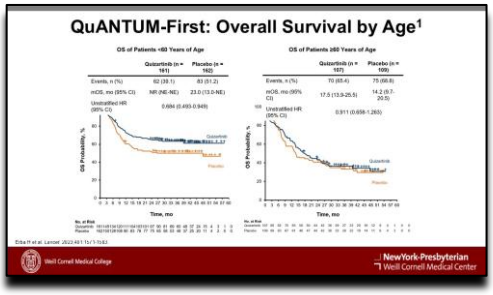
Midostaurin (Rydapt®), as you can see, has a significant side effect profile; and this is likely due to the fact that it targets other receptors besides FLT3, as I had mentioned earlier. So, at some point, patients will experience nausea, or vomiting, or diarrhea, or just some sort of GI upset. And it's very difficult for them to sometimes stay adherent to the medication. We can see headaches, and fluid retention, and sometimes changes to your blood sugars so be mindful of patients who maybe have diabetes at baseline.
We try to monitor liver function labs and QTc as mentioned. And in some small set of patients in clinical trials, there were some pulmonary toxicities. But again, this was very rare; and it is hypothesized to be due to an off-target effect in midostaurin (Rydapt®). So, we don't really see this that often in practice.



Slide 36: QuANTUM-First: Addition of Quizartinib (Vanflyta®) Improves OS vs Placebo in ND *FLT3*-ITD+ AML[1]

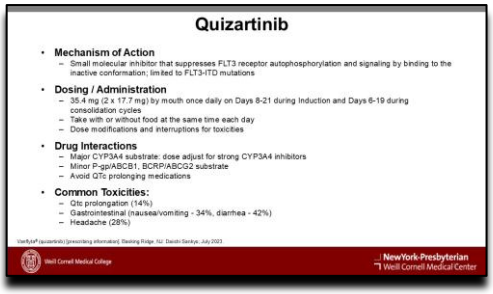
Dr. Desai: So, midostaurin (Rydapt®) was the first drug that was approved and the second FLT3-ITD targeted drug is quizartinib (Vanflyta®). This was based on the QuANTUM-First study which improved survival compared to placebo in newly diagnosed patients with FLT3-ITD-positive AML. It's important to note here that It does not work against FLT3-TKD mutations. So, if someone has a FLT3-TKD mutation, the standard choice is midostaurin (Rydapt®). If somebody has an ITD mutation, then we have two drugs approved – midostaurin (Rydapt®) and quizartinib (Vanflyta®). Both were randomized against placebo. Quizartinib (Vanflyta®) improved survival compared to placebo, as you see, 31 months compared to 16 months.

QuANTUM-First enrolled a wider range of patients from 18 to 75 while the RATIFY study only included 18 to 60. So, this is one place where even elder patients were approved; and there was a survival benefit overall in the study. There was a 22% reduction in risk of death with the addition of quizartinib (Vanflyta®) compared to placebo.



Slide 37: QuANTUM-First: Overall Survival by Age[1]

Now, when you look at the subgroups of less than 60, which is sort of the valid comparison to midostaurin (Rydapt®), quizartinib (Vanflyta®) improved survival compared to placebo. And in over 60, although this subgroup, again, it was not always powered, but the subgroup showed it was similar. The point is that over 60 patients did tolerate quizartinib (Vanflyta®) well, and usually in fit people we would give the drug and at least there's data in this age group, so this is where I would generally prefer quizartinib (Vanflyta®). While under 60 in ITD, you have a choice between quizartinib (Vanflyta®) and midostaurin (Rydapt®). And both are not randomized to each other; so, there are, many things we think about in choosing between midostaurin (Rydapt®) and quizartinib (Vanflyta®). But the point is both are available and have shown improved survival.

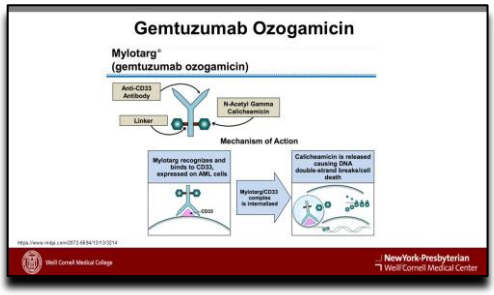


Slide 38: Quizartinib (Vanflyta®)

Dr. Johnson: So, quizartinib (Vanflyta®) made its debut formally from an FDA approval perspective in July 2023; but quizartinib (Vanflyta®) has been around for some time. And so back in the day when they did study quizartinib (Vanflyta®), they didn't use the correct dose; and they noticed that there was dose-dependent toxicities and they needed to have closer monitoring. So, with the newest trial that just came out, we have appropriate dose that is very well-tolerated for patients above and below the age of 60.

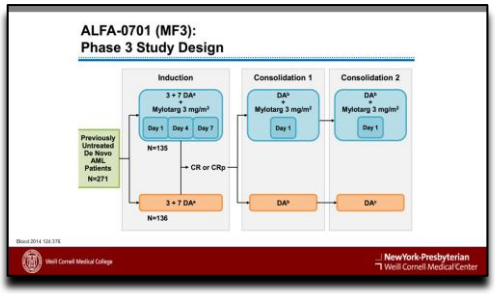
So, the dose of which you start really depends on what phase of treatment, the drug interactions that are involved, as well as their baseline QTc. But the typical starting dose is 35.4 milligrams once a day for 14 days on days 8 to 21. And as you can see, there's already a difference in administration versus midostaurin (Rydapt®), which was twice a day. Patients can take it with or without food, but it's important to take it around the same time each day.

One of the similarities that quizartinib (Vanflyta®) has with midostaurin (Rydapt®) is that it is also a CYP3A4 substrate. But what's nice is that there are very clear dose reductions and clear instructions on how to manage these drug interactions as well. It's important we monitor QTc at baseline and frequently throughout and try to minimize again other concomitant QTc prolonged medications to avoid any risk of arrhythmia, cardiac events. And other things to counsel your patients on are nausea, vomiting, diarrhea, or headache.



Slide 39: Gemtuzumab Ozogamicin

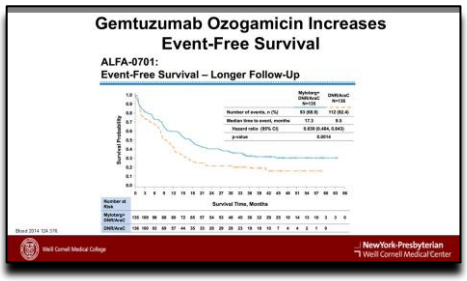
Dr. Desai: So, we have covered our FLT3-mutated subgroup. What about some other subgroups, the other intermediate risks? So, one of the other backbone drug that we add to 7+3 is gemtuzumab ozogamicin. This is an anti-CD33 antibody which is linked to calicheamicin. Calicheamicin is very toxic, otherwise given IV. But because this is sort of targeted against and linked with CD33 antibodies, it is able to release specifically in CD33-positive AML blasts, which is very common. Most AML do have CD33-positive disease. And the intention is to have like a payload that kills leukemia in addition to a backbone of therapy.



Slide 40: ALFA-0701 (MF3): Phase 3 Study Design

So, this was approved based on the ALFA-0701 study where a de novo patient, so again, de novo, not secondary patients. De novo AML patients who are given 7+3 as the backbone, gemtuzumab was given as, day 1, 4, 7. And the standard arm, obviously, did not get the drug; and it was also given for consolidation on doses.

Again, it's a little bit out of scope to discuss the variations in which you can actually give this drug. But we have changed our practice in when to give gemtuzumab but based on to avoid sort of toxicities, predicting who will go to transplant or not because there is veno-occlusive disease that's associated with the drug. So, my point is that the drug can be added to the backbone.

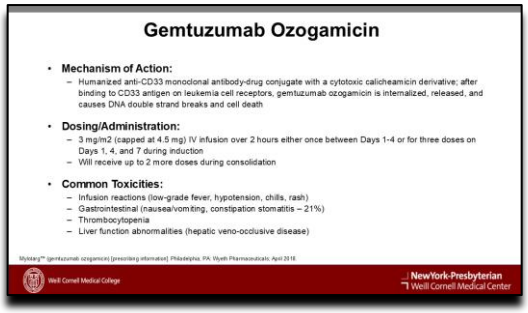


Slide 41: Gemtuzumab Ozogamicin (Mylotarg®) Increases Event-Free Survival

And what this drug showed, there was an improved event-free survival, not overall survival, but event-free survival advantage to the addition of gemtuzumab ozogamicin (Mylotarg®) compared to this sort of standard 7+3 without G-O or GO, however you want to call it.

Now there are many subgroups within this study; and if you look at this very, very carefully, it does not work in the adverse risk. So, even if somebody has de novo and they have adverse cytogenetics, there is absolutely no improvement in that, so we do not give this in that subgroup. In people who have favorable karyotype, it has made the most impact with survival rates over 10% more than 7+3, so this is absolutely the standard of care in somebody who has favorable risk or binding factor leukemia specific to core binding factor leukemia. Adding gemtuzumab ozogamicin (Mylotarg®) into 7+3 is considered standard.

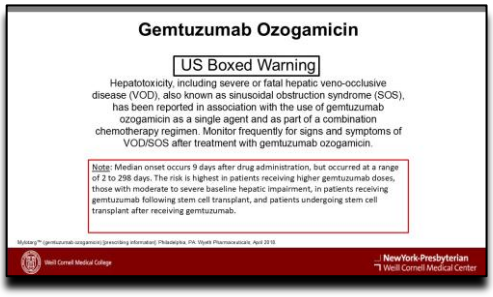
In the intermediate other patients, so not bad cytogenetics, not core-binding factor, the rest of the catchall AML, it does increase event-free survival. So, some centers may add this, and some consider this as it didn't improve overall survival; so, there may be other things we want to consider like molecular mutations and this and that. But, it is approved for, from, an FDA standpoint, for both core binding factor leukemia and intermediate-risk AML to add to the backbone of 7+3.



Slide 42: Gemtuzumab Ozogamicin

Dr. Johnson: So, gemtuzumab is a two-hour IV infusion; and, again, depending on the protocol your institution follows, at least one dose is given during induction and then up to two more doses during consolidation cycles. We typically cap the doses to protect patients from the toxicities, specifically veno-occlusive disease.

From a side effect perspective, it's generally well-tolerated. There is some potential for nausea or constipation and stomatitis again because of that calicheamicin component. Patients should just be mindful of any bruising or bleeding when they have thrombocytopenia. And then if they were to experience an infusion reaction, sometimes that can present as a low-grade fever, low blood pressure, chills, or hives. But that's really rare because we do give about three medications prior to the infusion to prevent this. The one toxicity that Dr. Desai had already alluded to, that's somewhat unique to gemtuzumab, is a specific type of liver toxicity, specifically called hepatic veno-occlusive disease.

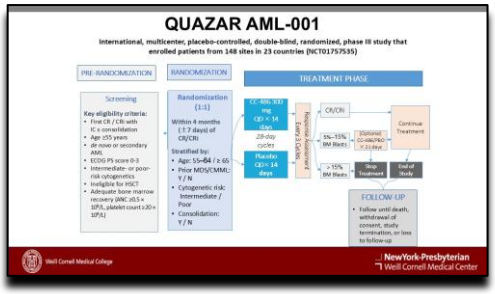


Slide 43: Gemtuzumab Ozogamicin

There is a black box warning for hepatotoxicity associated with gemtuzumab, and this is a life-threatening condition. The other name you can hear about this is sinusoidal obstructive syndrome. Although the, in studies the median onset's about nine days, VOD can technically happen at anytime on or after treatment, even up to day 300.

In most studies, the actual incidence is less than 5% to 10%; but then they noticed that the risk was higher in patients who received extremely high doses, uncapped doses, the ones previously referenced and back in the day. Patients who have baseline severe hepatic impairment, if they are receiving a stem cell transplant or they've already received a transplant, or they received alkylator therapies, these are the patients that we have to be mindful of and are at higher risk for VOD. So, it's important to evaluate with each patient if they're a good candidate or not, review their liver function labs closely, and monitor for signs and symptoms of VOD, which can include ascites and weight gain.

Dr. Desai: So this is actually what I spoke in the past, that when you have a good risk AML, because they're less likely to be transplanted, it's better to, we use this very confidently to improve survival and there's no risk of VOD in transplant because we don't transplant these people generally. But it's the intermediate risk that we're going to transplant somebody, then maybe you don't want to pick a GO-based regimen because there is this risk of VOD, particularly in the post-transplant setting.



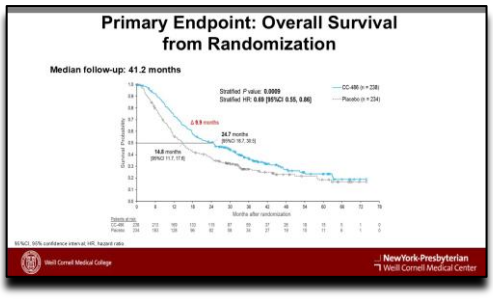
Slide 44: QUAZAR AML-001

So, let's say these, so we talked about all of this backbone of 7+3. We add the FLT3 inhibitors. If they have a FLT3 mutation, we do liposomal daunorubicin and Ara-C (cytosine arabinoside). If it is secondary, we add the GO if you have good risk and we consider it in select patients with intermediate.

So, what happens once they are in remission. We finish the consolidation or we go for transplant. Now, transplant is simple. They go for transplant, and nothing happens after, other than post-transplant follow-up. But if they decide not to go for transplant, what do we do? Is there something maintenance in patients with AML?

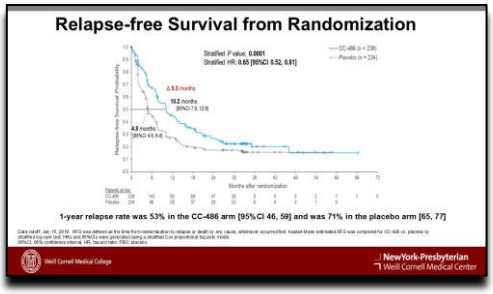
So, this is, maintenance AML was approved based on the QUAZAR study. This was an international multicenter study. Patients who were in remission, either just in remission with chemo and not had consolidation therapy or received consolidation therapy and then one way or the other decided not to go for transplant. This is important. Doesn't replace a transplant. It just is telling that if the clinical judgment is that the patient should not go to transplant, then this is an option. Okay.

Patients were over 55. They had to have intermediate- or poor-risk cytogenetic category that we discussed previously. They were randomized to placebo versus oral azacitidine (Onureg®), which is the drug CC-486. Oral azacitidine (Onureg®) was continued in 28-day cycles until either death, withdrawal of consent, or relapse, or loss to follow-up.



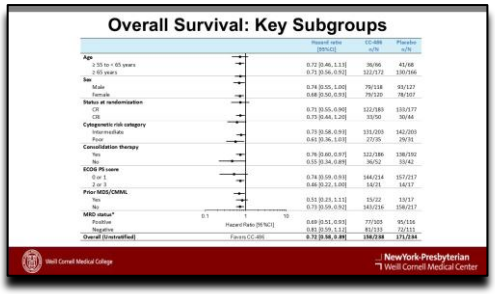
Slide 45: Primary Endpoint: Overall Survival from Randomization

And what the trial showed was a significantly improved survival benefit to oral azacitidine (Onureg®), 24.7 months versus 14 months, and the drug was approved for maintenance therapy in AML based on this study.



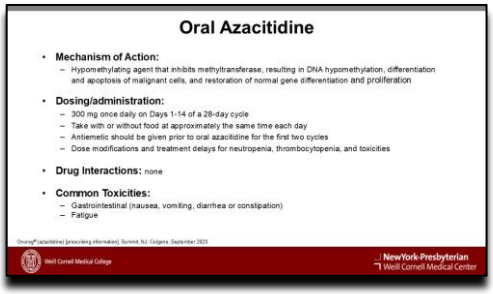
Slide 46: Relapse-free Survival from Randomization

There was also improvement in relapse-free survival with one-year relapse rate of 53% in the oral azacitidine (Onureg®) arm and 71% in the placebo arm.



Slide 47: Overall Survival: Key Subgroups

Within subgroups, even if you had previous AML, CMML, MRD status, all of them generally favored the maintenance therapy. So, this usually works in all subgroups. The only potential place where we are not completely sure is if somebody has already had four cycles of consolidation. I think the significance was sort of a little bit less but again better than doing nothing because they're not transplanting, and then they need a drug to sort of maintain the remission.

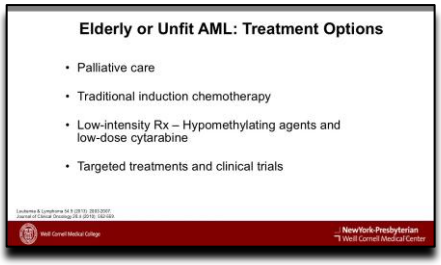


Slide 48: Oral Azacitidine (Onureg®)

Dr. Johnson: Oral azacitidine (Onureg®) in the maintenance space should be dosed at 300 milligrams once daily on days 1 to 14 of a 28-day cycle. It's important knowing that it is a moderate emetic potential. Patients should be receiving one antiemetic such as ondansetron (Zofran®) prior to the first two cycles. If you're not having any chemotherapy-induced nausea/vomiting, then just keep it on an as-needed basis. But if you are still experiencing nausea and vomiting, please continue to take ondansetron (Zofran®) 30 minutes prior.

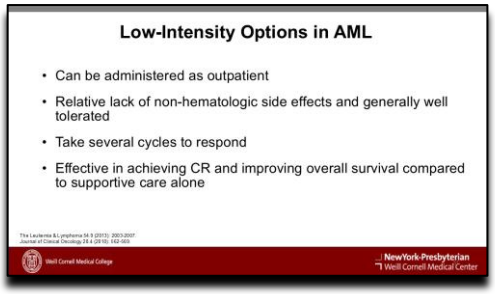
In most patients it's well tolerated, but if there are any significant toxicities, such as nausea or vomiting or reduced blood counts, providers may consider modifying the dose or delaying treatment until recovery. Of note, this agent does lack any clinically significant drug interactions because it undergoes hydrolysis, and it's not really involving the CYP3A4 pathway. So, it's easier from an administration standpoint.

Dr. Desai: One more thing I would like to add is that this is different pharmacokinetically than subcutaneous or IV azacitidine (Onureg®), and they should not be mixed with each other. Maintenance is oral azacitidine (Onureg®). It's supposed to be more continuous exposure, while IV or subcutaneous azacitidine (Onureg®) has a very different kinetic profile; and it is not to be used as maintenance in lieu of oral azacitidine (Onureg®).



Slide 49: Elderly or Unfit AML: Treatment Options

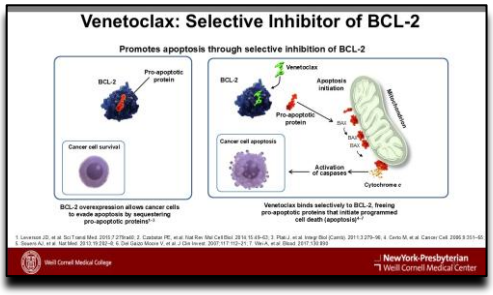
So, we covered the fit elderly, or young fit patients. So, what about elderly people or unfit AML? What do we do, and what are the options for treatment?



Slide 50: Low-Intensity Options in AML

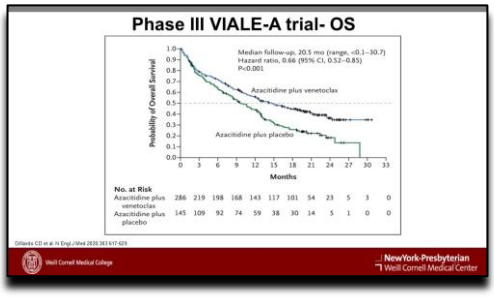
So, lower intensity treatments have been the backbone. The two big lower intensity therapies were low-dose cytarabine and hypomethylating agents. In the US, hypomethylating agents, either decitabine (Dacogen®) or azacitidine (Onureg®), have been more used as sort of the backbone of lower intensity therapies in AML. This is usually given as a single agent. It's given outpatient. These drugs have less hematologic toxicity; but they do take several cycles to respond.

So, as a single agent, for example, hypomethylating agents usually take at least two to four cycles before they really will start kicking in. The goal is to get into a remission and then improve survival by not having these cytopenias from AML if they do go into remission as a single agent, the response rate is somewhere between 20% to 40% with hypomethylating agents.



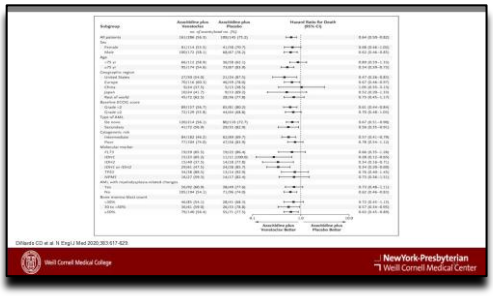
Slide 51: Venetoclax (Venclexta®): Selective Inhibitor of BCL-2

That was our old past. Now we have made progress in this. The biggest, biggest improvement in the elderly setting came with the advent of venetoclax (Venclexta®), which is a BCL-2 inhibitor. This is very commonly now used as sort of the backbone of HMA-based therapy. Venetoclax (Venclexta®) binds selectively to BCL-2, and it frees pro-apoptotic proteins that then initiate programmed cell death. It is synergistic with hypomethylating agents by itself. Venetoclax (Venclexta®) doesn't work that well. It's about 20% response rate, but in combination with hypomethylating agents, there is a lot of synergy.



Slide 52: Phase III VIALE-A trial- OS

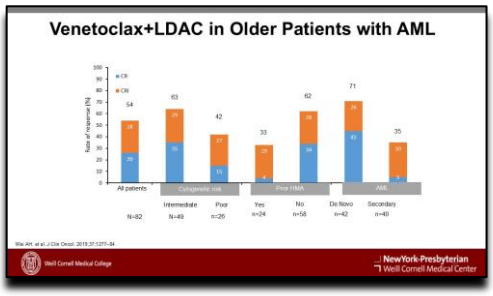
The Phase III VIALE-A study is what led to the approval of hypomethylating agents and venetoclax (Venclexta®). This was azacitidine (Onureg®) plus venetoclax (Venclexta®) compared to azacitidine (Onureg®) plus placebo. The remission rate is approximately about 70% with the combination on an average compared to the 20% to 40% that we were given with single-agent azacitidine (Onureg®). Median follow-up at 20 months, there was an improvement in survival; and that's why this drug was approved and is the most commonly used backbone.



Slide 53: Graph

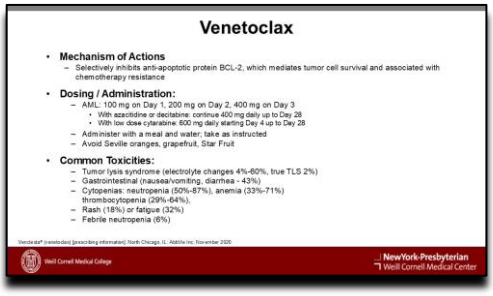
Again, without going into too much details, several subgroups were checked, and the drug it generally works in all of the subgroups, including IDH-mutated, as well as NPM1-mutated AML.

The two places where it might work a little bit inferior, compared to some of the other core mutations, is perhaps FLT3 and TP53 here. The survival may be a little bit less, so now there are advents of newer therapies that we try to use. But generally, as a backbone HMA, venetoclax (Venclexta®) is the current standard of care.



Slide 54: Venetoclax (Venclexta®)+LDAC in Older Patients with AML

Low-dose cytarabine can also be combined with venetoclax (Venclexta®), but this Phase III trial was negative. There were many reasons for that, but, in general, if somebody has had previous hypomethylating agent, it's possible to just switch the backbone to a low-dose Ara-C (cytosine arabinoside) and venetoclax (Venclexta®)-based regimen. For example, if they had MDS already, had HMA exposure, so that could be the backbone. But, frontline otherwise patients, hypomethylating agent and venetoclax (Venclexta®) is, is the standard.



Slide 55: Venetoclax (Venclexta®)

Dr. Johnson: Yes, so venetoclax (Venclexta®) is definitely active in a lot of different hematologic malignancies besides AML. So, we're going to focus on the dosing of AML specifically. It's just important to note that depending on what indication your patient is on, you have to be thoughtful about what dose and the ramp-up that they're going to receive.

Typically, AML patients are initiated on 100 milligrams on day 1,200 milligrams on day 2, and then 400 milligrams on day 3. Most commonly, we'll have these patients on a hypomethylating agent like Dr. Desai said. So, their maintenance dose will continue to be 400 milligrams up to 28 days. But if you're receiving low-dose cytarabine injections, then the maintenance dose is technically 600.

As we continue to use venetoclax (Venclexta®) more frequently, we know that not all patients require 28 days. So, it's very oftentimes we use 14 days, 21 days, etc., depending on the patient and some of their molecular cytogenetic changes as well.

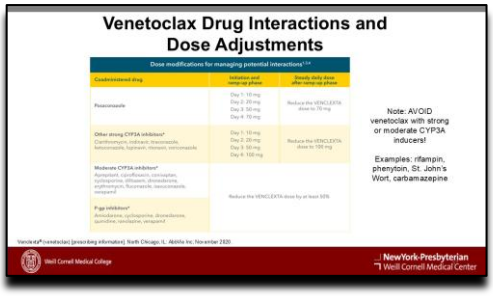
It's important that patients remember to take venetoclax (Venclexta®) with food and water, and we know that high fat meals helps with increased venetoclax (Venclexta®) absorption. But at the same time, you also want to tell your patients to avoid specific fruits that contain CYP3A4 enzymes such as grapefruit, star fruit, and Seville oranges.

The dose and duration of venetoclax (Venclexta®) is subject to change with each cycle either based on drug interactions, the tolerability, or the response that you have. So, one of the things I always tell my patients is that it's important to take the medication as instructed by the oncologist rather than how it's written on the prescription bottle because there could be medication errors that can occur.

So, your pharmacist should be reviewing all the current medications as well as any future anticipated medications to make sure that there's no clinically significant CYP3A4 or P-gp interactions that require either a dose adjustment or a modification of therapy.

So, then the question is why do we dose escalate this way for venetoclax (Venclexta®); and the reason for that is really to prevent a condition called tumor lysis syndrome, and that occurs because of the breakdown of leukemic cells and the release of those contents into the bloodstream. So, in most cases, it manifests as just changes in electrolytes or uric acid, so you'll see high uric acid, potassium, and/or phosphorous, or potentially low calcium. But if these substances stay in your body and they form crystallized products, they can get stuck in the kidneys and by them staying in the body longer, it can cause issues if you don't prevent it appropriately. And we want to prevent that, such as acute kidney injury, arrhythmias, and urological side effects. And your risk of TLS really depends on your degree of disease burden. So, in clinical studies when they looked at AML and venetoclax (Venclexta®), it was just more common to see just the electrolyte changes, and only 2% of patients truly had manifestations of tumor lysis. And the reason why we only see such a small percentage is because we prevent it very well by hydrating patients and giving medications to reduce uric acid.

So, it's important to be monitoring these labs closely and slowly increase the dose over time to avoid TLS. Other toxicities are just nausea, vomiting, diarrhea, cytopenias, rash, and fatigue.



Slide 56: Venetoclax (Venclexta®) Drug Interactions and Dose Adjustments

As I mentioned, venetoclax (Venclexta®) is a major CYP3A4 and P-gp substrate, so we have to be thoughtful of any inhibitors and inducers that could be involved in the patient's medication list. And we either have to reduce the dose of venetoclax (Venclexta®) or identify an alternative medication that lacks this interaction. When possible, we try to avoid newly initiating one of these type of inhibitors until after the ramp-up is complete. But if they're already started on one of these medications, the ramp-up dose is quite different; and it's listed here for your reference.

So, strong CYP3A4 inhibitors such as posaconazole (Noxafil®) and voriconazole (Vfend®) require close to 75% dose adjustment. But for patients on posaconazole (Noxafil®) specifically, the package insert will recommend reducing the dose to 70 milligrams. However, in clinical practice, most of our providers, as Dr. Desai might say, we just use 100 milligrams; and this is because venetoclax (Venclexta®) is usually available in 10, 50, and 100 milligram tablets. So, to take 70 milligrams would mean three tablets, and you can imagine the room for medication error that can happen.

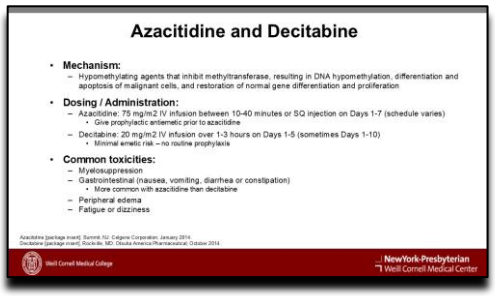
Dr. Desai: The other important point thing here is that venetoclax (Venclexta®) is like one drug where there is so much change that can happen on the, almost on a day-to-day basis in terms of like the dosing. We don't even give it for 28 days anymore. We do 21, 14 days. That is drug started and stopped.

This is one place where there's a lot of art to venetoclax (Venclexta®) management, and this is very, very important and really difficult to hone down because it's not just about con-meds. It's about knowing the patient as well their disease burden. They had baseline creatinine elevation. We don't want to upset the balance too much. So many times, we use Hydrea® (hydroxyurea) to bring down the white cell count before we really begin. And there is a lot of questions on this all the time, both, from even to the pharmacy, from even when their patients leave the hospital. And very, very important that this is managed well because you can really, really induce very significant myelosuppression by just making a mistake on a con-med and not recognizing that the patient was started on something as simple as Coreg® (carvedilol), which, many times their cardiologist or whoever would just start and will completely knock off patients' counts.

Dr. Johnson: So, it's really important that not only do we have drug warning wards, but we also talk to the physicians and our other groups to see like what medications we really need to keep on board and versus other medications that we can really find alternatives for.

The modern CYP3A4 inhibitors, in my experience, sometimes get missed because not a lot of providers are thinking about other medications like our cardiac medications, like Dr. Desai was saying. Carvedilol (Coreg®), we have diltiazem (Cardizem®). We also have amiodarone (Pacerone®) as well, and these require 50% reduction.

Unfortunately, unlike our strong and modern CYP3A4 inhibitors and P-gp inhibitors, we don't have formal dose adjustment recommendations for our CYP3A inducers, and this includes rifampin (Rifadin®), phenytoin (Dilantin®), St. John's wort, or carbamazepine (Carbatrol®). So, in this particular scenario, the manufacturer recommends avoiding altogether. If you notice that one of your patients is on any of these particular medications, it's important to alert the oncologist to see if there is an appropriate alternative or if therapy can be temporarily held while on venetoclax (Venclexta®).



Slide 57: Azacitidine (Onureg®) and Decitabine (Dacogen®)

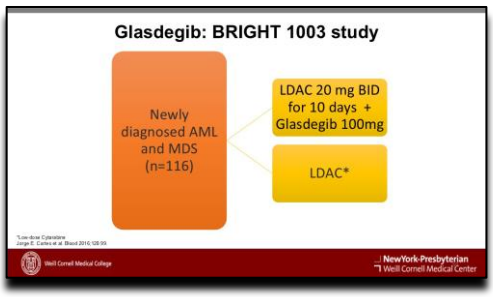
Dr. Desai: So this, again, I think is pretty standard treatment, azacitidine (Onureg®) and decitabine (Dacogen®), which we give as backbone. Both drugs are used for AML management and can be given outpatient. And the only point I'll make here is although azacitidine (Onureg®) and decitabine (Dacogen®) can be given outpatient when it's combined with venetoclax (Venclexta®), we actually prefer admission in the hospital, especially for our very elderly patients because of the risk of tumor lysis and everything.

And the original trials also required hospitalization, so I always point this out that when we say it's a lower intensity treatment, it doesn't mean that it doesn't need hospitalization. You really should be hospitalizing some of the old, especially the very elderly patients for the combination.

Dr. Johnson: I absolutely agree. Like when we see our patients both on azacitidine (Onureg®), on venetoclax (Venclexta®), our patients still will experience febrile neutropenias, the toxicities like the myelosuppression, the GI side effects. So, it's something we still have to account for.

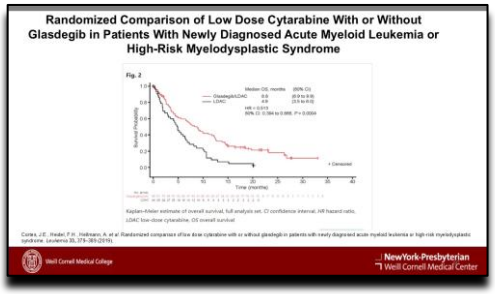
One of the main differences I would say with azacitidine (Onureg®) and decitabine (Dacogen®) is also the emetic potential risk. So, with azacitidine (Onureg®), you can see that we give a prophylactic antiemetic 30 minutes prior, such as ondansetron (Zofran®), versus decitabine (Dacogen®). And since it's minimal emetic potential, there's no routine prophylaxis required. And as Dr. Desai mentioned in a previous slide, we have oral azacitidine (Onureg®), and that's not to be interchanged with azacitidine (Onureg®) here,

either IV or subcutaneous. We pick between the two formulations based on patient preference, and decitabine (Dacogen®) is only available as IV.



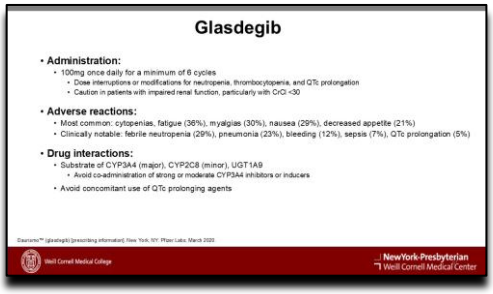
Slide 58: Glasdegib (Daurismo™): BRIGHT 1003 study

Dr. Desai: So, going to talk about this in passing. The other drug that is also approved in combination with low-dose cytarabine is glasdegib (Daurismo™), which is given with LDAC 20 BID for 10 days, randomized, to low-dose Ara-C (cytosine arabinoside) alone.



Slide 59: Randomized Comparison of Low Dose Cytarabine With or Without Glasdegib (Daurismo™) in Patients With Newly Diagnosed Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome

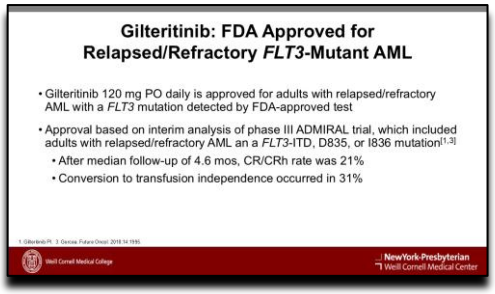
There was an improvement in survival with the addition of glasdegib (Daurismo™). However, the response rate to this drug is lower; so HMA and venetoclax (Venclexta®) gives a complete remission rate of almost 70% to 80%, while glasdegib (Daurismo™) combinations will give it at 38%. So, we don't really use this so much in, in upfront management, but this is here just for completeness sake that this is approved for frontline AML.



Slide 60: Glasdegib (Daurismo™)

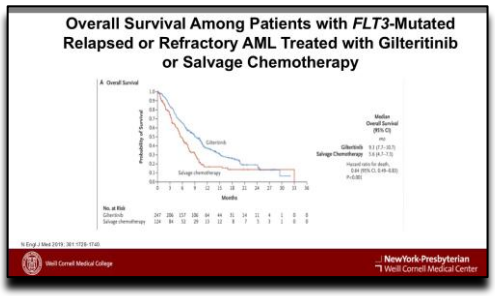
Dr. Johnson: Yeah, I would agree with Dr. Desai. In our clinical practice we have so many other options right now with better response rates and better toxicity profile that also avoid some of these drug interactions that are listed here on the slide, so glasdegib (Daurismo™) has really fallen out of favor for upfront.

But if you were to give it, just note that it's 100 milligrams once daily for about six cycles because it does take some time for these drugs to work. And please be mindful of patients who already have baseline kidney dysfunction.



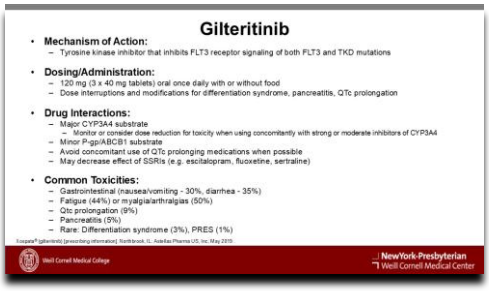
Slide 61: Gilteritinib (Xospata®): FDA Approved for Relapsed/Refractory *FLT3*-Mutant AML

Dr. Desai: So now, switching gears to relapsed and refractory disease, and we'll go to frontline in just a minute because I wanted to keep at the targeted agents sort of separately. Gilteritinib (Xospata®) is FDA approved for relapsed and refractory FLT3 AML. The frontline trial adding 7+3 plus gilteritinib (Xospata®) has completed enrollment, but it is not yet reported, so we don't know what, what'll happen to that. But it is available and approved for, in the relapsed setting based on a Phase III ADMIRAL study which enrolled patients with relapsed/refractory FLT3-ITD or TKD mutations. And it's given as a single agent daily. The CR rate was about 21%, and 30% approximately patients had transfusion independence.



Slide 62: Overall Survival Among Patients with *FLT3*-Mutated Relapsed or Refractory AML Treated with Gilteritinib (Xospata®) or Salvage Chemotherapy

The way the trial was run, gilteritinib (Xospata®) was given as a single agent; and the randomization was with anything the investigators wanted, including salvage chemotherapy. And it, as a single agent, without any chemotherapy backbone showed improved survival and hence this is sort of the standard in relapsed setting.

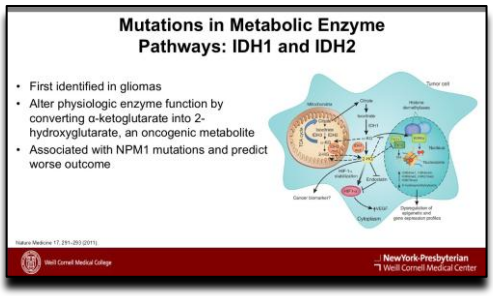


Slide 63: Gilteritinib (Xospata®)

Dr. Johnson: So, gilteritinib (Xospata®) targets both ITD and TKD mutations. The typical dose is 120 milligrams, and similar theme that you're seeing is that this is also a major CYP3A4 substrate, so just be mindful of drug interactions as well as any other medications that prolong the QTc.

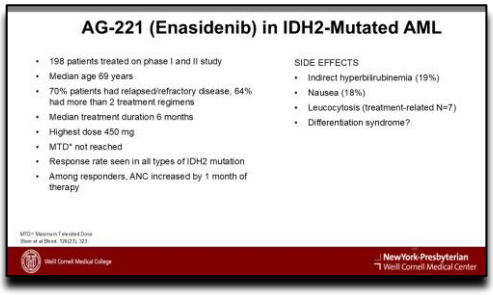
Another unique thing to remember with gilteritinib (Xospata®) is that there could be a potential reduction in efficacy when taking gilteritinib (Xospata®) with drugs that target your serotonin receptors such as escitalopram (Lexapro®), fluoxetine (Prozac®), and sertraline (Zoloft®). Some of the other side effects with gilteritinib (Xospata®) include increased transaminases, muscle or joint aches, fatigue, and headache. Patients should get a baseline CPK and QTc check prior to starting treatment and at specified intervals throughout.

We do see some nausea, vomiting, and diarrhea; but in clinical practice, we actually see this to a lesser degree than, let's say, midostaurin (Rydapt®), for example. And I think this can be attributed to the fact that gilteritinib (Xospata®) doesn't have those other off-target effects that midostaurin (Rydapt®) does as well.



Slide 64: Mutations in Metabolic Enzyme Pathways: IDH1 and IDH2

Dr. Desai: The other targetable mutations are IDH1 and IDH2. This gives me nightmares from medical school. The entire Kreb cycle, which I thought was totally pointless, came back to haunt me when IDH inhibitors came across and was approved in AML. But anyways, the IDH1 and 2 mutations cause a change in the enzymatic function converting alpha-ketoglutarate to 2-hydroxyglutarate, which is an oncologic metabolite and causes a differentiation rest. Having mutations that target this pathway will stop this effect and causes sort of the differentiation to happen and ultimately these cells would undergo apoptosis with time. IDH1 and 2 are associated with NPM1 mutations. By themselves, they are associated with worse outcomes. But with the onset of all these IDH mutations, that is changing.



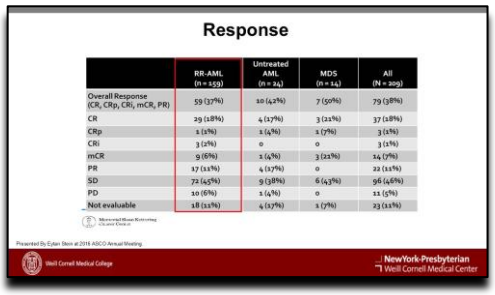
Slide 65: AG-221 (Enasidenib) (Idhifa®) in IDH2-Mutated AML

For the IDH2-mutated patients, enasidenib (Idhifa®) is currently approved based on 198 patients treated both relapsed/refractory and frontline were actually part of this trial because it was so targeted in approach. The,response rate generally was about 40%, and the drug is actually approved for both frontline and relapsed patients with IDH2-mutated AML. But because the HMA-venetoclax (Venclexta®) combination achieves such a higher CR rate, most people tend to prefer HMA-venetoclax (Venclexta®) as the frontline option and reserve the IDH2-mutated agents like enasidenib (Idhifa®) in the relapsed setting.

What's important is you can have indirect hyperbilirubinemia with this drug, particularly if you have the UGT1 path, you know, SNP that is associated with this. It's not harmful to the patient, but it's just something to watch for. We tolerate it up to a certain point, but, but if the patient is turning yellow, you'll have to kind of dose reduce a little bit.

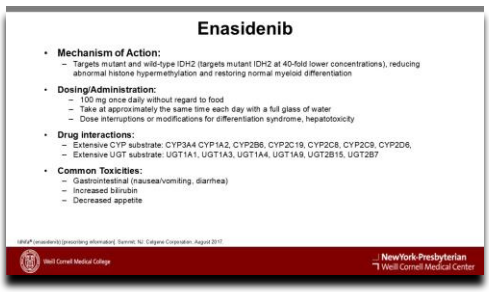
Differentiation syndrome is very, very important. It can cause death, so it's very important to recognize it. It is unique to these differentiators or IDH-mutated drugs. Patients can present with a high white cell count and fluid retention either overall in the body or in the

lungs or ascites. But sometimes it can be very subtle. It can come without a high white cell count. It can just be fluid. Sometimes it just manifests as sudden onset AKI, so suspicion is always high when a clinical status is changing. Always think about differentiation syndrome. It is treated with steroids. We can bring down the white cell count with Hydrea® (hydroxyurea). Sometimes you have to hold IDH inhibitors, but generally recognizing it is the most important thing and starting steroids right away so there is a black box warning about it. It's important to let the patients know as well that because these are oral drugs, they're sitting at home taking it, they really have to call us with any change in clinical, status, water retention. We generally tell them to take weights every couple of days just to see sort of the early differentiation effects, which could be manifested as just weight gain. So that's something to always look for.



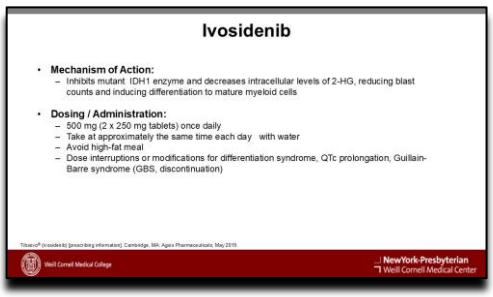
Slide 66: Response

As I said, response rates overall was somewhere in the 40% for both relapse/refractory and untreated AML.



Slide 67: Enasidenib (Idhifa®)

Dr. Johnson: So, enasidenib (Idhifa®) is our IDH2 oral inhibitor. It's usually dosed at 100 milligrams once daily and this should be given with water but without regards to food. This medication does undergo extensive hepatic metabolism, as Dr. Desai was mentioning, the UGT systems and things like that, which is why you might see that increase indirect bilirubinemia. But even though you see these extensive lists of substrates, they're not clinically relevant, so there's not actually a lot of drug interactions we need to be worried about. You might see some decreased appetite and some GI side effects but otherwise very well tolerated. And like Dr. Desai mentioned, for the next few drugs, we should just be monitoring for differentiation syndrome.

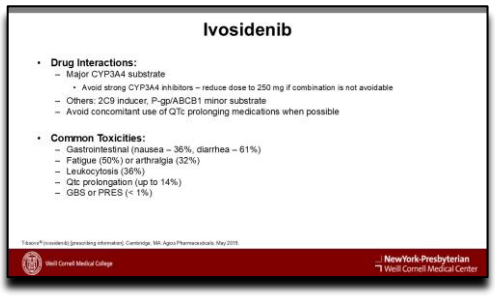


Slide 68: Ivosidenib (Tibsovo®)

Dr. Desai: In the same lane, ivosidenib (Tibsovo®) is approved for treatment of IDH1-mutated patients. This is also based on a trial that looked at mostly in the relapsed setting. The response rate is about the same, about 35% complete remission rate. The important thing about both ivosidenib (Tibsovo®) and enasidenib (Idhifa®) is as a single agent, it can take a

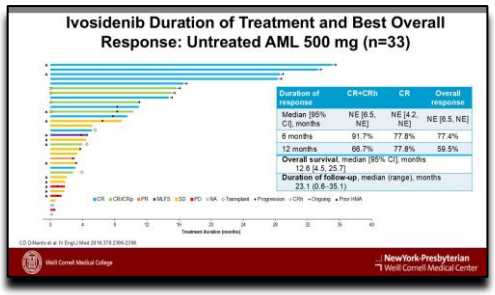
long time to work. You really have to give drug for about six months before you really say that it's not working. So, it's important to set the expectation to the patient that you've got to keep taking the drug for six months. And some of these complete remissions happen over a course of time for taking the drug for that long, as long as six months.

Dr. Johnson: Yeah, so as Dr. Desai mentioned, it's very important that patients are adhering to their therapy. Ivosidenib (Tibsovo®) is convenient in the fact that it is once a day. You want to take it around the same time each day and try to avoid a high-fat meal. There are some drug interactions that we have to think about, but mainly just avoid medications that have QTc prolonging effect. And we will talk about the side effects in the next slide.



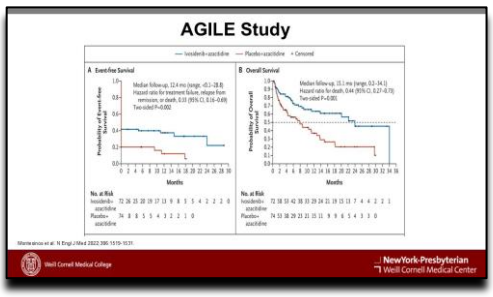
Slide 69: Ivosidenib (Tibsovo®)

In terms of side effects, really monitoring and counseling your patients to notice any fatigue, any muscle aches, GI side effects as well. We mentioned that leukocytosis can be secondary from differentiation syndrome, but patients don't oftentimes notice that. That's usually with laboratory values changing when they come into clinic. QTc prolongation, again, like we said, will be monitored with medications and other assessments throughout treatment.



Slide 70: Ivosidenib (Tibsovo®) Duration of Treatment and Best Overall Response: Untreated AML 500 mg (n=33)

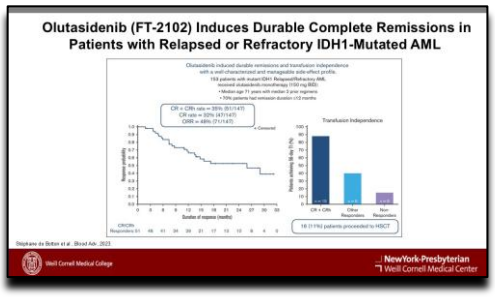
Dr. Desai: We talked about this already, upright ivosidenib (Tibsovo®) response rate.



Slide 71: AGILE study

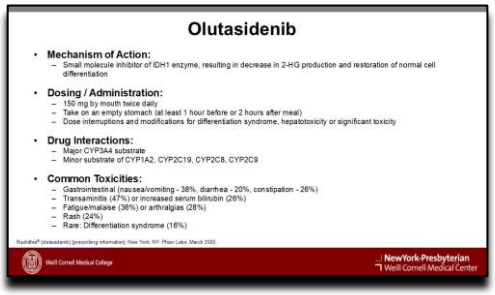
But I want to focus on the AGILE study which was a more recent study that was published here. IDH-mutated patients frontline, so not relapse, frontline. Newly diagnosed patients was given the combination of azacitidine (Onureg®) plus ivosidenib (Tibsovo®) versus placebo plus azacitidine (Onureg®), and there was a significant overall survival with the combination of ivo plus azacitidine (Onureg®).

So, this regimen is approved for frontline IDH1-mutated patients as well. This is only for the IDH1. The enasidenib (Idhifa®), but it's the IDH2 mutation, is not approved for frontline in combination with azacitidine (Onureg®). That trial was not done. But here it is approved, so these patients have a choice of either having HMA-venetoclax (Venclexta®) or HMA plus ivosidenib (Tibsovo®) for the IDH1-mutated, and again, which to pick is a whole discussion which we will not get into. But the point is both of these regimens are appropriate for this.



Slide 72: Olutasidenib (Rezlidhia®) (FT-2102) induces durable complete remissions in patients with relapsed or refractory IDH1-mutated AML

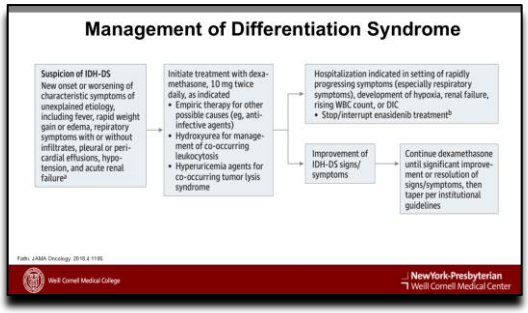
The IDH1-mutated drug that was also approved is olutasidenib (Rezlidhia®). This was also, like people who are IDH1 relapsed/refractory, some patients who had previous ivosidenib (Tibsovo®) were also included in this study. And there were responses seen in that group as well who had previous ivosidenib (Tibsovo®), didn't respond, went onto olutasidenib (Rezlidhia®) and had a response. Again, similar overall complete remission rate was about 35%. Overall response rate about 48%, and about 10% were able to go into transplant. So olutasidenib (Rezlidhia®) is approved in the second-line setting or relapsed/refractory setting for this indication of IDH1-mutated patients.



Slide 73: Olutasidenib (Rezlidhia®)

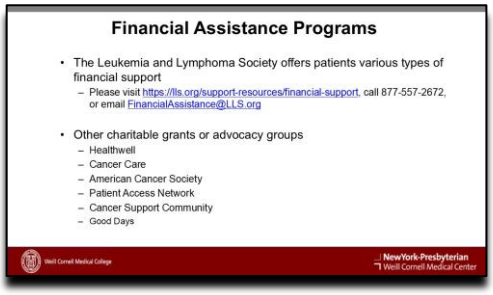
Dr. Johnson: So olutasidenib (Rezlidhia®) being approved in December of 2022 actually opened up a lot of options for patients who still had an IDH1 mutation, even if they were exposed to previous IDH inhibitor therapy. It's important that you counsel your patients when they're taking their medication, 150 milligrams twice a day, to take it on an empty stomach, so that's ideally one hour before or two hours after a meal because these high-fat meals can actually increase the drug levels and cause side effects.

There are some CYP3A4 drug interactions to be mindful of and, again, similar to other IDH inhibitors, we should be monitoring for signs and symptoms of differentiation syndrome. Otherwise, the other things to look out for are elevated liver function tests, fatigue, muscle aches, nausea and vomiting.



Slide 74: Management of Differentiation Syndrome

Dr. Desai: I think we talked about this as well, management of differentiation. Recognizing it, leuko reduction, making sure there are other reasons. See, one thing I'll say here is that sometimes we're not sure that it's differentiation syndrome. It might be that the patient's just progressing from leukemia or has an infection. You just do all of it like you would rather overtreat differentiation syndrome than undertreat differentiation syndrome; but the point is to always tell the patient. We give them like cards to monitor differentiation syndrome, recognize it, early treatment. We usually don't have any issues. We've not had a death in our hands, but again, this has been reported in the community where there were deaths on the drug when patients were sitting at home.

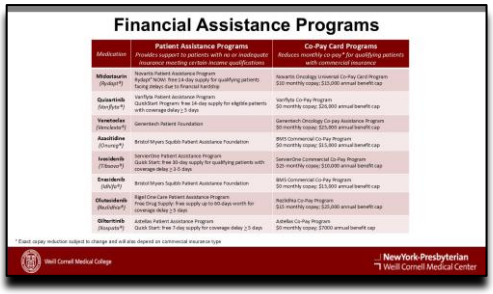


Slide 75: Financial Assistance Programs

This is one place where we would so be lost without our pharmacy colleagues, once we prescribe, like how do you actually get the drug? Catherine, you want to take this one?

Dr. Johnson: Yeah, absolutely. So, as Dr. Desai was mentioning, as much as we can talk about these oral chemotherapy agents, accessing them and making sure patients are adhering to them is important. Sometimes this, the adherence is not actually just related to the toxicities, but it also comes sometimes because of financial reasons and their inability to receive the medications because these medications, as you can imagine, have a very significant out-of-pocket expense because of the high cost. So, as your pharmacist, we can play a role in not only identifying but also helping patients and find the right financial assistance programs that are right for them, depending on their scenario.

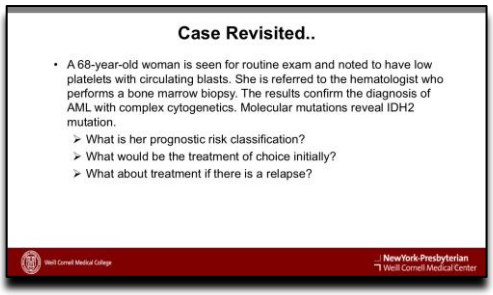
The Leukemia & Lymphoma Society also has several resources available to help patients navigate this process while they're already dealing with so much on their own. And they can provide various forms of support themselves. There are also other charitable grants and advocacy programs available to help you find the help you need.



Slide 76: Financial Assistance Programs

There are typically two types of financial assistance programs, whether it's copay cards or patient assistance. The table here just lists some of the sponsored programs available. I won't go in depth, but I just want to kind of highlight the main differences that you might encounter. For patients with insurance, but they have a high copay, there might be a copay card program that you could be eligible to enroll in, and this can significantly reduce your monthly payments to as little as $0 a month. Whereas patient assistance programs, whether it comes from the manufacturer or these charitable organizations that we mentioned in the other slide, these are for patients who have either no insurance or they have inadequate coverage and they meet certain income qualifications to receive free medication.

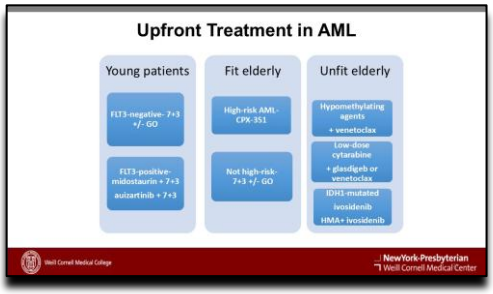
Patients usually don't qualify if they have government insurance such as Medicare, and you typically need to reapply on an annual basis. And then in some cases where if you're having insurance coverage delays, some of the manufacturers have a quick start program because as we've been mentioning, adherence and no delays in treatment are very important to us. So, they will be able to supply some medication if you absolutely need it.



Slide 77: Case Revisited..

Dr. Desai: So, let's revisit the case that we talked about earlier. This is a patient who had an AML with complex cytogenetics and has an IDH2 mutation. So, her prognostic ELN risk is adverse. This patient is at high risk for relapse. And because she has the complex cytogenetics, which is considered MDS defining, the initial treatment of choice could be liposomal daunorubicin and cytarabine (Vyxeos®); and that could, could be a good option.

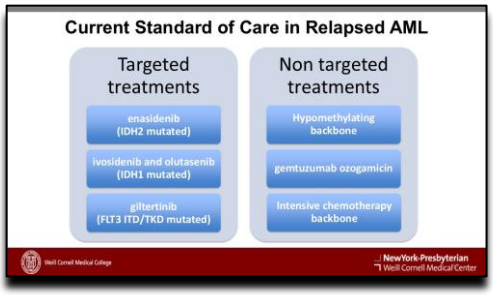
Again, if you give 7+3, you know, it's an approved agent. But I think that most people would prefer, as we talked about, liposomal cytarabine and daunorubicin (Vyxeos®). If this patient were to relapse, this patient should be transplanted after receiving a CR. But if they were to relapse, the other agent that's approved here is enasidenib (Idhifa®) because she would have an IDH2 mutation. It is important to recheck the IDH2 mutation at the time of relapse because sometimes you do lose it if it's a different clone that's relapsing. But that would be the sort of standard approach.



Slide 78: Upfront Treatment in AML

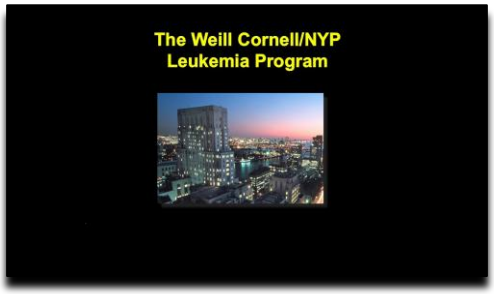
To sum up sort of our, everything that we talked about, so in young patients, if somebody's FLT3-negative, the backbone is 7+3 +/- gemtuzumab ozogamicin. Again, preferred for core binding factor. For intermediate risk, it's an option. For FLT3-positive, , if you have an ITD mutation, you could have both midostaurin (Rydapt®) and quizartinib (Vanflyta®) in combination with 7+3. If you have a TKD mutation, then the standard is midostaurin (Rydapt®) plus 7+3.

In fit elderly patients with high-risk AMLs, again, CPX-351 (Vyxeos®) or liposomal daunorubicin, this is also actually approved for younger people. If there's a 30-year-old who comes with therapy-related, they can get this as well. If they're not high risk, then again 7+3 +/- GO is an option. In unfit elderly, HMA plus venetoclax (Venclexta®) is the commonly used regimen. Again, low-dose cytarabine and +/- glasdegib (Daurismo™) or venetoclax (Venclexta®) is potentially an option; but most people would use HMA and venetoclax (Venclexta®). For IHD1-mutated patients, you could use ivosidenib (Tibsovo®) plus HMA as frontline management. And in relapse setting again, it all depends on what they have.



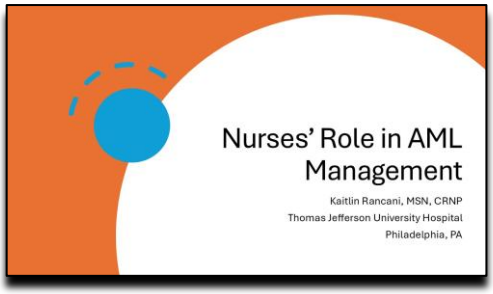
Slide 79: Current Standard of Care in Relapsed AML

If you have relapsed AML and they have a targeted agent that works – enasidenib (Idhifa®), ivosidenib (Tibsovo®), olutasidenib (Rezlidhia®), and that's absolutely the standard of care. For FLT3 it's gilteritinib (Xospata®), both ITD and TKD. If patients don't have any of these targetable mutations, then you could use many other regimens – intensive chemotherapy, other hypomethylating backbone clinical trials. Gemtuzumab ozogamicin (Mylotarg®) is also approved for, as a single agent for relapsed disease. Again, not to be used in adverse risk disease, but it's theoretically available for these patients as well.



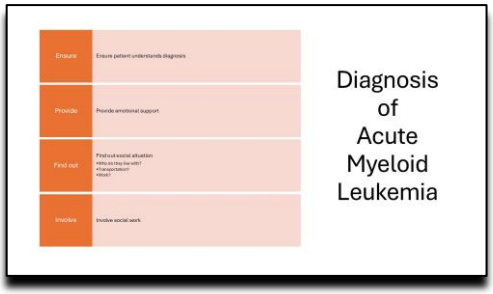
Slide 80: The Weill Cornell/NYP Leukemia Program

And with that, I think we end our program. I cannot stress how much the cooperation and close connection with physicians and pharmacists are in getting our patients everything they need throughout their course with their AML treatment.



Slide 81: Nurses' Role in AML Management

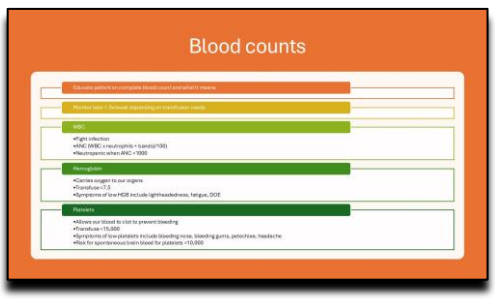
Hi, my name is Kaitlyn Rancani. I'm a nurse practitioner at Thomas Jefferson University Hospital. And today I'd like to talk to you about the nurse's role in the management of patients with acute myeloid leukemia.



Slide 82: Diagnosis of Acute Myeloid Leukemia

So once a physician meets with the patient and gives them the diagnosis of AML or acute myeloid leukemia, it's really important for the nurse and or nurse practitioner to kind of go into the room following the doctor. And you want to just ensure that the patient understands their diagnosis and make sure they understood what the doctor told them, ask them if they have any additional questions regarding their diagnosis.

Often times, you go into the room and there's additional thoughts and questions that the patient has. So it's a good time to just ensure that the patient understands everything. And with that, you want to provide some emotional support, let the patient know that your team is there for them and will help them through this difficult time. And next, you want to find out the patient's social situation. So it's really important to find out who the patient lives, with what type of transportation that they have. If they take the bus there, then that might be an issue. And they might need some resources to help with transportation and also what line of work they do. So if they work from home, maybe they can still continue to work. If they have kind of a labor job, then they won't be able to do that. So we can fill out their FMLA paperwork and disability forms and again, help decide what resources they need. And finally, it's really important to involve social work kind of along the lines above. It's important to provide any financial resources and support groups that might be available to the patient.



Slide 83: Blood Counts

Next, whether you do it at the visit with diagnosis or kind of when they begin treatment, one of the things you really want to teach your patient about is about their blood counts. So their CBC becomes one of the most important things during this time. So you want to educate a patient on what a complete blood count is or a CBC and let them know that we're going to be monitoring their labs one to three times a week, depending on transfusion needs.

I usually explain to patients that their white blood cell count is the cells that are used to fight infection. We often monitor and follow their ANC, which is their absolute neutrophil count, to see how high risk for infection they may be. And you can see the calculation of that on this slide. And educate the patient that they become neutropenic when their ANC is below 1,000. So sometimes when they're diagnosed, their ANC is already below 1,000. But definitely during treatment, their ANC will drop and they will be at high risk for infection. I let them know that their hemoglobin is the cell that carries oxygen to our organs and to our body. We usually provide blood transfusions when their hemoglobin is below 7.5.

And I educate them on the symptoms of low hemoglobin, which is light-headedness, fatigue, dystonia on exertion. Any just overall weakness can be a sign that their hemoglobin is low, which again is expected to happen during treatment if it's not already present on diagnosis. And finally, I educate patients that their platelet count is very important as this is the cells that clot our blood and prevent bleeding. So we usually transfuse platelets when your count is less than around 15,000.

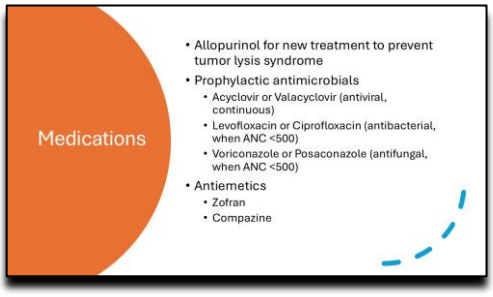
Symptoms of low platelets include nose bleeding, bleeding gums, petechiae, or a headache. And the headache is really important because when a patient has a platelet count of less than 10,000, they are at very high risk for a spontaneous brain bleed. So I don't want to scare the patient, but it's important for them if they don't usually get headaches, if they have a terrible headache that they really need to call and report that symptom as they probably need an urgent head cat scan.

Slide 84: Treatment

And then you want to go over the treatment with the patient. So sometimes a patient may need to go into the hospital to get their chemotherapy. We're doing a lot more without patient treatments with AML, but there are still some regimens that you need to be in the hospital for. So it's important to just kind of inform them on what to expect. Sometimes patients are there for four to six weeks, know, basically until count recovery and to bring things to the hospital that make them comfortable and just, make sure that they are prepared for that.

If it's an outpatient treatment, you want to provide the schedule, the treatment time, how long they'll be in the infusion center, what to bring with them, what to expect during that time. You want to decide if the patient will need a PICC line. So sometimes it's recommended because it's a lot of blood sticks and IVs, even with the transfusions following treatment. But there is one particular chemotherapy that requires a PICC line and that is Vixios. So that needs to be given through a central line. So that's important to remember. And then they also may need an echocardiogram prior to starting treatment, especially if a drug could be cardio toxic. We give them a lot of chemotherapy education,

some printouts, just some verbal talk about the exact side effects of the drugs that they're getting. You want to provide education on the supportive medication that they need. And if you can provide a calendar, that would also be very helpful for the patient.

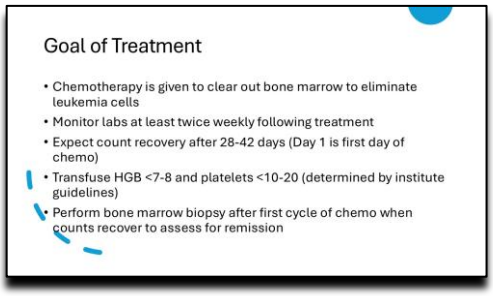


Slide 85: Medications

Some of the medications they need kind of upfront before they get begin treatment. One is called allopurinol. This is for a new treatment of AML. It helps prevent tumor lysis syndrome by decreasing the uric acid in their blood. Usually patients need this for about two to four weeks during that initial treatment. When patients have a low white blood cell count, they are required to take some preventative antimicrobials. They are going to take acyclovir or valacyclovir, which is an antiviral. This helps prevent shingles. You want to educate them that they will take this continuously. It will not stop. Whereas if they take levoquin and ciprofloxacin, those are antibacterial and usually we give them for an ANC less than 500. They will remain on these antibiotics until their blood counts recover. Once the ANC is kind of trending up and goes above 500, then they can stop this antibiotic.

The same thing for an antifungal. Our preferred antifungals are boriconazole or posiconazole. This helps prevent a fungal lung infection. And again, we give this when their ANC is below 500.

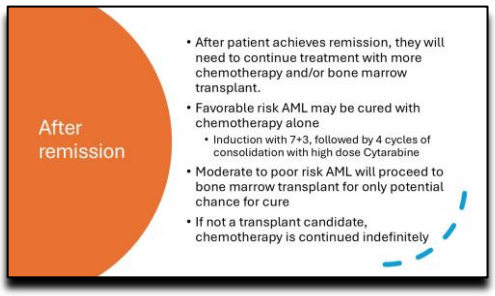
And then they will be prescribed anti-nausea medications such as Zofran and or Compazine. These are kind of the two primary anti-medics that are used, but of course there is a whole arsenal of anti-nausea medications that can be used and you should let the patient know that if these drugs don't work that they should let you know.



Slide 86: Goal of Treatment

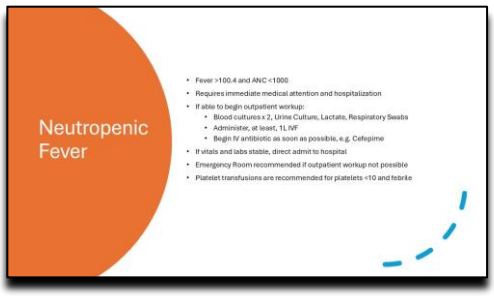
So the goal of treatment, so patients frequently need this kind of repeated to them so they understand what's happening, especially once they're in week two or three of not feeling well and having low blood counts, they start to get frustrated. They don't really understand what's happening. So you have to remind them that the goal of the chemotherapy that you're giving them is to clear out their bone marrow because we want to clear out the bad cells. And unfortunately with that comes the good cells get cleared out too. So we're going to monitor their blood counts at least twice a week following treatment. Their counts will drop. They will require blood transfusions. It's important to prepare them for this. If their counts are really low, sometimes patients are in our office three to four times a week. So day one is the first day of chemotherapy.

And they can expect to see count recovery after day 28 to 42. Following their count recovery is when a bone marrow biopsy gets performed to assess for remission. So overall, this is always kind of the plan of the very first cycle of treatment. And we really want to get them into a remission, so it's really important to prepare for them for this timeline and what to expect during this time and that it's normal.



Slide 87: After Remission

So after remission, so after we do that first bone marrow biopsy and our patient achieves remission, they will need to continue treatment with more chemotherapy and/or proceed to bone marrow transplant. So sometimes people have favorable risk AML that can be cured with chemotherapy alone. The common treatment for this is induction chemo with seven and three followed by four cycles of consolidation with high dose cytarabine. More often or not though, patients do have moderate to poor risk AML and they do need to proceed to a bone marrow transplant as their only potential for cure. If they are not a transplant candidate, they will continue chemotherapy basically until that treatment stops working or they progress and then we can hopefully have other lines of therapy in place.



Slide 88: Neutropenic Fever

One of the biggest things to remind your patients of, and this is, I tell patients, if you remember nothing else, remember this. If you get a fever over 100.4, you need to go to the hospital. Patients that have low white blood cell counts are really high risk for infection and sepsis and just getting sick really quick. So it's important for them to know what to do and you need to know how to help monitor your patients during this time. So we educate patients to check their temperature twice a day in the morning and the evening, or if they're not feeling well. If they have a fever over 100.4, they should call the office. This does require immediate medical attention and hospitalization. We've gotten really good at kind of beginning a workup for the patient in our outpatient office. So if it's during a workday, patients come into our office.

We obtain labs like standard labs, CBC, CMP, look over everything. And you also want to get blood cultures, a urine culture, draw the lactate and do any respiratory viral swabs. And then we get them to the infusion center and we want to give them at least a liter of fluid. If they show signs of sepsis, then it's usually more than that. And we begin an antibiotic as soon as possible.

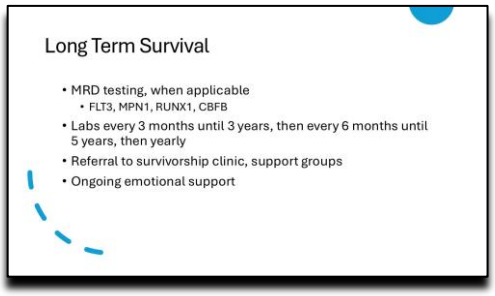
Ideally, if you can begin an antibiotic within one to two hours of the onset of a fever, it really helps improve patient outcomes. As long as their vitals and labs are stable, we're

able to call in a direct admission to the hospital. This allows the patient to avoid going to the emergency room, which is both helpful for the ER and really is much more satisfactory for the patient. Unfortunately, this isn't always how things work out.

So if the outpatient workup is not possible, whether it's late in the day or if it's overnight or on the weekend, then the emergency room is recommended. And sometimes this comes up while a patient's in the infusion center with a fever and the nurses will ask, the infusion nurses will be like, is it OK to proceed with the platelets? If somebody's platelets are under 10 and they are febrile, they do have a much higher risk for bleeding, such as brain bleed it is okay to go ahead and give platelets.

Slide 89: Oher Common Side Effects

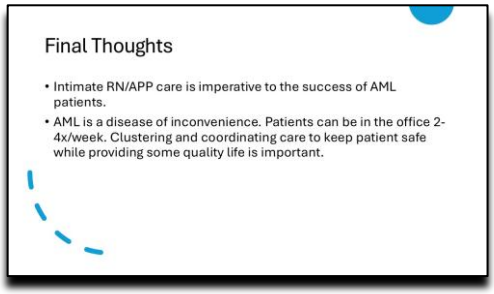
Some other common side effects that can occur are nausea, vomiting. Again, we talked about using Zofran and Compazine. Again, if those aren't working, there's other medications that can be used such as Ativan. We also use Fenergan or Zyprexa. But basically I tell patients, or I try to let them know that they really, given all the drugs that we have nowadays, they shouldn't experience and suffer from nausea and vomiting. So they just need to let us know what's working and what doesn't work. A lot of patients do get mucositis due to their neutropenia. So it's really important to explain and educate them on oral hygiene. So saltwater rinses, magic mouthwash can be used and kind of just helping support them through this uncomfortable time. You can use pain medicine if needed. And just, you know, anything liquid they can get down is definitely more important than food during that time. And usually the mucositis gets better once the white blood cell count gets better. And sometimes patients do have diarrhea. It's really important if they're neutropenic and having a lot of diarrhea, you want to rule out any infectious source, one being C. diff and if that's all negative, then you can recommend antidiarrheals like Imodium.



Slide 90: Long Term Survival

So long-term survival, when patients do become long-term survival patients, whether they're finished, they're initial treatment of just chemotherapy for a cure. And sometimes after a bone marrow transplant, as far as their leukemia goes, sometimes we are able to do minimal residual disease testing. So that's done on the blood. It's only for the mutations listed below with FLT3, MPN1, RUNX1, and a CBFB. But that can be sent on their peripheral blood work just to help monitor for a deep remission. Usually, we obtain their labs every three months until three years, and then every six months until five years, and then yearly. We usually like to see our patients every year, even if they're beyond five years. But if they

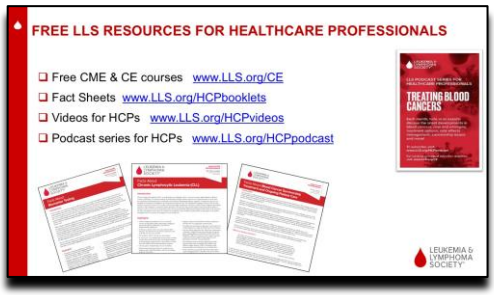
choose to just follow with a primary at that time, just remind patients it's important to get a CBC yearly because unfortunately you do have a risk of developing a secondary AML or another hemolymphagy due to the chemotherapy that you got. So at least a CBC yearly is important. And then a lot of institutes have implemented survivorship clinics. So a referral to survivorship clinic is good and support groups. Sometimes it's kind of at the end of treatment when everything settles down that patients really begin to suffer from anxiety due to their treatment, kind of like a PTSD. So providing support groups and emotional support to help the patient kind of move on and get reintegrated with normal life is really important.



Slide 91: Final Thoughts

Some final thoughts. It's a high touch. RN/APP care is imperative to the success of AML patients. So we are really talking to our patients three to four times a week. If they're not feeling well one day, a phone call to follow up the next day is important. Monitoring their blood counts closely. This is how we prevent hospitalizations and really help increase the success of their treatment as well as their quality of life. And unfortunately, AML is a disease of inconvenience. So patients can be in office two to four times a week, whether it's appointments for your team or for another team, trying to cluster and coordinate care to keep the patient safe while providing quality of life to them and to their family members who are often accompanying them to their appointments is really important.

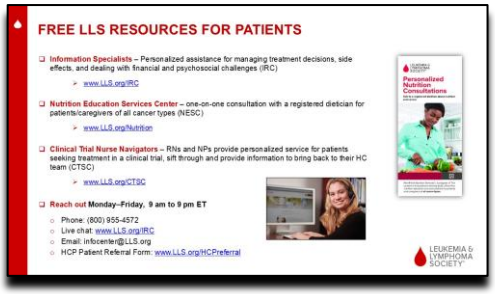
And finally, just collaborating with the team of pharmacists and physicians. We work very closely with our whole collaborative team and that gives patients a lot of support and education and always making sure we're giving the right information and doing the right thing.



Slide 92: Free LLS Resources for HealthCare Professionals

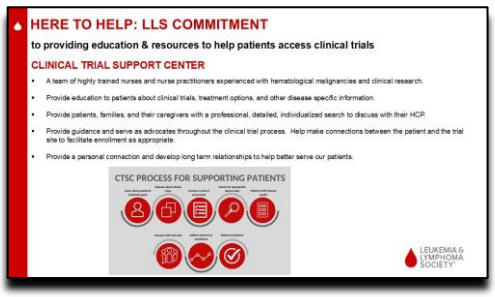
Thank you to our faculty for your informative and interesting presentations. I am now pleased to share brief information about resources for you and to share with your patients.

The Leukemia & Lymphoma Society offers free CE and CME online webinars such as this one, in-person regional programs, and a podcast channel for healthcare professionals, where you can listen to discussions on treatment, side-effect management and more. New and interesting topics are added every few weeks. Access these, as well as videos and fact sheets for HCPs at the link on this slide.



Slide 93: Free LLS Resources for Patients

LLS Information Specialists are highly trained oncology social workers and nurses who provide accurate, up-to-date disease, treatment and support information, including financial, in 1 to 1 conversation with patients. Patients can contact them directly, or you can complete a referral form. They can also help you order free copies of booklets to give to your patients. LLS offers free nutrition consultation to patients and caregivers w/any cancer diagnosis in a 30-minute phone call with one of our registered dietitians. Contact them using the information listed here to refer a patient. Our Clinical Trial Support Center Nurse Navigators are RNs & NPs with expertise in blood cancers. They work 1 on 1 with patients, via telephone, to provide user friendly information, help find appropriate clinical trials and personally assist them throughout the clinical trial process and provide info for the patient to bring back to their healthcare team. They also work with healthcare professionals. This is unique service from LLS and I hope you will consider all of these Specialists as an extension of your Team.



Slide 94: Here to help: LLS commitment

Here is a brief overview of the Clinical Trial Support Center Process for Supporting Patients. The Goal is NOT to enroll every patient into a trial, rather to increase opportunities for participation by facilitating informed decision making & minimizing logistical barriers for the patient. They work in collaboration w/the patient's healthcare team to decide if a clinical trial is right. Ultimately, they educate, support, and empower patients to be active participants in, & have control over their treatment decisions.

Slide 95: Free LLS Resources for Patients and Caregivers

LLS offers blood cancer disease specific information & support resources for patients & caregivers, including telephone & web education programs, videos, podcasts & booklets. I encourage you & your colleagues to stay up to date on the availability of LLS' Financial Assistance programs, & other resources, using links in these slides.

Slide 96: Free LLS Resources for Your Patients

We are committed to addressing needs of minoritized and underserved communities impacted by a Blood Cancer, including those facing barriers to optimal care. Our booklets are available in English & Spanish, and our Informational Specialists, Clinical Trial Nurse Navigators, and Registered Dieticians, consult with patients in several languages.

Slide 97: Thank You

Thank you again to our faculty and thank you to all the healthcare professionals listening. I hope the information will be helpful to you, as you care for your patients. If you would like more information for yourself or support for your patients, please contact an Information Specialist at The Leukemia & Lymphoma Society at 800.955.4572 www.LLS.org/support