A Deeper Dive into Advanced and Future Directions in Treating Patients with Acute Myeloid Leukemia

Sandra E. Kurtin, PhDc, ANP-C, AOCN®, and Gabrielle Zecha, PA-C
The University of Arizona Cancer Center, Tucson, AZ, and The University of Washington, Seattle, WA

SANDY Good evening, everyone. We are proud of you for staying awake this late on a school—oh, it's not a school night, is it? It's a weekend. So, we're so glad you could join us for this accredited program tonight called "A Deeper Dive into Advances and Future Directions in Treating Patients with Acute Myeloid Leukemia." It is accredited by the Annenberg Center for Health Sciences at Eisenhower and to claim your credit, please follow the instructions on the sheet you received this evening. If you didn't receive an instruction sheet, let a staff member know and they can provide one for you.

We're going to get started. I'm Sandy Kurtin. You may have heard me earlier today. I am a nurse practitioner at the University of Arizona Cancer Center. And I'm going to let Gabe introduce herself.

GABRIELLE My name's Gabrielle Zecha; I'm a PA at the Seattle Cancer Care Alliance in the University of Washington Medical Center.

SANDY All right. And with that, let's get started. Let me ask, first of all, how many of you attended the session with Dr. Artz and Dr. Ridgeway? Okay, that's helpful. I'm going to try to really put a little different twist on this so we're not—not that reinforcement isn't a good thing, but I don't want to make it repetitious.

I'm going to take the time to go through a little bit of the science and the A to Z of acute leukemia, so we're going to start really talking about those things. We're going to go through a little bit about the disease state. Acute leukemias were first noted by Dr. Virchow in 1845, so these have been around a long time. And yet, we've had the same therapy for a very long time since then, so it's exciting to be up here to talk about some of these new developments.

There are roughly 21,000 cases each year. Unfortunately, about half of the people die, so it's never good when you see incidence in death rates being that close together. Median age at diagnosis is 68, so this is really important to keep in mind. And the 5-year overall survival for all comers is really pretty dismal; when you think about malignancies, really only 27 percent. In terms of new cases and deaths, again, you can see how those look and how close those are in proximity. That's never really what we're looking at. Median age at diagnosis, 68. Most of the people who are dying are a little older than that, so the median age at death is 78.

Most of the time, we don't know what causes this; it's more common in older patients. We get hematopoietic senescence, so as we get older, the organs don't repair themselves readily and you can have abnormalities occurring as a result of age itself, mutagenic and genotoxic stresses.

We heard a lot about the driver mutations, but also acquired mutations in many of the talks that we've heard so far. And then, we cause it sometimes ourselves by treating people for other diseases, and this is becoming more and more of a problem. The big players here are therapeutic alkylators, so drugs like

cycloheximide, which is probably still today one of the most common drugs that we administrator; the topo II inhibitors, which include things like the anthracyclines, mitoxantrone, and etoposide; and then, doing stem cell transplants. So we have secondary leukemias, treatment-related AML, or treatment-related MDS as a result of prior therapies in these patients with solid tumors.

There is a smaller number of patients who have ALL that then, as a result of their long-term therapy, develop AML. We see environmental and occupational exposures; one of the big culprits is benzines. Benzine is also the primary agent in tobacco, so we now have clear data to say that tobacco smoke is related to bone marrow disorders, and the myeloid diseases are not an exception.

We also see this phenomenon of AML that comes out of antecedent hematological malignancies—the most common one being MDS—also, representing a unique challenge, and then, very rare inherited congenital abnormalities.

Most of the time, onset here is pretty abrupt. I was at an advocacy meeting and talking to patients, and it's like you just get plucked out of your life. It's like boop, here you go; boom, right? And your life changes forever; it's very abrupt. Things have to happen very quickly. People often present with pretty dramatic symptoms. In some cases, we see skin involvement, so I'll show you a couple of pictures in a minute.

It's really important to talk about the history of the disease and how it presents and what kinds of things that you're seeing, so you get a little sense of

the tempo of the disease. AML, just like many of these hematological malignancies, is pretty heterogeneous, and you can really get a sense of how that's going to go by getting the sense of tempo. How long have they had these symptoms? Did it just happen a week ago or has this been cultivating over the course of several weeks? So, really looking at that carefully; looking at their comorbidities and medications is going to be critical as we initiate therapy, and needing to really take care of that whole patient and then doing a very good, thorough physical exam; full skin, the whole thing, orifices, everything.

Laboratory analysis is really critical in these patients as well. Patients with AML can present in active tumor lysis just from the disease itself, so we're going to want to do a baseline screen, including the uric acid and an LDH, which is not part of the complete metabolic panel; it's on a different instrument. The other thing to note is the LDH upper limit normal varies by institution, so there is no universal norm and that's important to know. Sometimes you'll see patients presenting with thermolysis, so we're going to want to look for that too.

In the case of APL, which we're not going to really talk about, some of these people present with coagulopathies and active DIC. So if there's some, but they're really just covered in bruises and they have like a bloody nose, you're going to be more worried about something like APL and we're going to want to do a full coag workup.

Lumbar punctures are absolutely necessary in ALL and anybody with CNS symptoms. With suspected myeloid malignancy, you're going to also want to do that. You're going to look for underlying viral entities. And then if they're young,

you want to make sure they're not pregnant. This has happened before and that's always very, very difficult.

Then you need the diagnostic bone marrow biopsy and aspirate, and this is really critical. And if you attended the session earlier with Dr. Artz and with Jean Ridgeway, you know that we have to ask the right questions. So when you're doing that marrow you've got to say, "What is my question? What are the things I might be looking for?" And make sure that you get a good sample and all of the different tubes that are necessary to answer any of those possible questions. It's really important to check with your team and really find out what do we think it might be? It's better to pour a little extra than not have enough. So, getting a good aspirate with spicules and then an adequate core—very critical to being able to answer the question.

Some of the things we want to know: we're going to do metaphase cytogenetics, which is basically those 20 metaphases. That's what you get in the bracket when you read a cytogenetic report; it'll say 16 out of 20 or whatever. If there's something that's greater than two metaphases, it's considered non-random, so it's real. There are transient cytogenetic abnormalities that happen in these malignancies just because there's so much going on. If it's less than two metaphases, that may not be real. We're going to screen for these genetic mutations.

It used to be that we asked for *NPM1, CEBPA, RUNX1,* and c-Kit, which is not on there, and those have now been trumped by some of these others: *TP53, ASXL1*, and *IDH2*. We're also going to ask some of the other questions in flow

cytometry now looking at CD33, which comes in the immunophenotyping. If you are concerned about APL, we're going to do PML RAR-alpha; that's a PCR test. And, also, if there's any concern for underlying CML, that if turned into blast crisis, you're going to do BCR-ABL. It's really important to just get a sense, and we do that from the history and the baseline laboratory analysis to get a sense of what is the question?

We're then going to do some diagnostic radiology. A baseline chest x-ray is always critical so that we have something that we know we started with. In case people develop symptoms, we can compare it to baseline—baseline EKG, MUGA, or echo—because anthracyclines are still very much a part of induction therapy in these patients.

If we're concerned about CNS disease or hemorrhage, you want a non-contrast CT. If you're worried about leukemic meningitis, then you need an MRI. Part of what we talked about in the imaging sessions is, again, what is your question? And if you're in doubt, call Radiology and say, "Here's what I'm worried about." And they're going to say, "Here's what you want to order," right? So we're not wasting time or money or unnecessarily exposing patients to the contrast dye and the radiation.

All of these people are going to need lines, so depending on what the possibilities are, what their platelets are, deciding what that line might be may vary. This is what the cutaneous manifestations could sometimes look like, and people that have monocytic predominance, it's a tissue infiltrating. They get these very hypertrophic gums to where they can hardly close their lips

sometimes and that's pretty telling. That actually can be good; that subtype of AML can actually be treated pretty effectively.

And then there are people who get leukemia cutis. And I've seen actually a lot of people who have relapsed with leukemia cutis where you start to see these bumps coming up into the skin, and that's really the first sign of relapse before we start to see some of the changes in their count. Always really important in these patients to do a good skin exam, a good oral exam.

We heard a little bit about the revision of the 2016 World Health Organization classification system. This is really getting complicated. It is not going to get any easier, so we've just got to keep hearing this stuff, to like strap on, hold on tight. It's like a bronco ride, right? Don't get bucked off. We can do it, right? We have to be able to understand this; it's very important in understanding prognosis. And we have to somehow be able to explain it to colleagues and to patients at some level.

They've broken this up into germline mutations with a predisposition for organ dysfunction and platelet disorders or myeloid neoplasm with predisposition and other organ functions. There's a bunch of these that have these molecular attributes attached to them.

And then you have AML with recurrent genetic abnormalities. And this is where you heard earlier that not only do you see the cytogenetic abnormality, but you see the associated molecular abnormality, and to really be able to fully characterize that patient's disease can take some time. These are not things that come back quickly, and that can be a challenge.

We've heard about AML with myelodysplasia-related changes. These are the people—you know, and these happen a lot. You have older patients, they come in, they look like they have acute leukemia de novo, like just leukemia. You treat that and then what's left is actually underlying MDS, and that changes the game completely. And then, of course, every category has a not otherwise specified. And then you get to this. This is how complicated this is getting. You're looking at these subtypes of these molecular attributes and you're basically carving out these little niches for these diseases. I will say that we don't completely understand all of these niches, but we're getting to a point where it's really becoming more and more clear.

So we use this for risk stratification. We want to know what are the factors associated with poor risk? How aggressive are we going to be with that patient? If they have AML from an antecedent hematologic malignancy, the prognosis is very different than if it's de novo. And certain types of de novo are considered like a core-binding factor AML. Translocation (8;21) is potentially curable. I've had people actually cured with standard therapy. You don't find those very often. Most people will not be cured without an allogeneic stem cell transplant. You can't have your own marrow when you have a myeloid malignancy. Well, you could, but it won't work, so why do it? You've got to have an allo in any myeloid malignancy.

So we look at all of these things to try to identify risk. We look at age alone. Age alone should not be a determining factor when—you know, those of you who attended the lecture earlier with the TOPS Clinic, really an innovative

way to look at—we tune people up so they're strong enough to be able to undergo this more aggressive therapy. But this is really just looking at this different AML based on age, and the difference that age alone makes in those patients when you look at 15 through 59 on the left there and then on the right age greater than 60. So even though we say age alone should not exclude treatment, it does matter in these patients.

They take all this information and they develop these risk categories. And here's the translocation (8;21) that's called core-binding factor; that's considered a favorable prognosis. But then you get into these mutated or unmutated *NPM1* and *FLT3,* and whether it's wild type or unmutated becomes very important, and I'll show you some examples.

Here's wild-type *NPM1* and *FLT3* internal tandem, or ITD high expression, and so, the combinations of certain things also matter. This is becoming very complicated and even the anatomopathologists are struggling to really embrace all this. It just was released really less than a year ago. It says 2016, but we really didn't get them.

Now this is a very eloquent body of work. This is Elli Papaemmanuil who is at Harvard and she has developed this extraordinary project. And we have an international working group for MDS; we have an international working group for MDS/MPN crossover; and then we have an international working group now in AML looking at bringing together samples from all over the world to be basically mapped and profiled. And so, this is just the beginning of this work; it's really extraordinary.

But what you can see here, the predominant driver mutations in AML, and what this tells us is we know there may be an opportunity there as a target for therapy. And some of these already are. And we know *TP53* is never good; it doesn't matter what you have, it's bad, bad, bad. *TP53* is 17p, that's your surveillance gene. If that gene is abnormal, you can't surveil your own abnormal cells. So 17p, *TP53* mutations or deletions are bad regardless of what it is. And you can see if you match those up with other abnormalities on the other axis there, that one line down there has a lot of problems.

This is where you start to look at matching these up. So, here's *TP53*, *NPM1*, and *FLT3*, and just by looking at whether it's a complex karyotype. A complex karyotype is greater than three abnormalities on metaphase cytogenetics, so your cytogenetics are basically your blueprint. If you have a bad blueprint, you are not going to make a normal cell. If you have a paragraph of cytogenetic abnormalities, that's bad, that's really bad. So, complex is just greater than three, so if you add a complex karyotype to the presence of *TP53*, look at the difference that makes in that outcome. So if *TP53* by itself is bad, but you add to that other abnormalities, and that makes it that much worse.

Similarly, you heard about *NPM1*, whether it's wild type or mutated, plus or minus the DNA methyltransferase or DMT3 mutation, and look at the difference that that makes in survival. So we're beginning to understand why there's patients that do good or well and then people that just do very poorly and they don't respond and they don't do well even with induction therapy.

Then we have our therapy-related myeloid neoplasms, and I talked a little bit about this. Alkylators are bad players. There's different times of onset; this is really devastating for people. So we see a lot of patients who have had R-CHOP, right? It's still the standard of care for diffuse large B-cell lymphoma. And they started developing cytopenias late in the game—you know, 8, 10 years out—and it's not their lymphoma coming back; they have treatment-related AML or MDS, and that's devastating.

Probably even more devastating are the patients that we're beginning to see with breast cancer and even ovarian cancer where we're having these topo II inhibitors and they're relapsing or they're developing treatment-related AML 2 or 3 years out from the treatment of their primary therapy for their other malignancy and they also have a very poor prognosis. So it's good now, but we have some options for these patients. It's really devastating for them.

This is how it looks: treatment-related AML, treatment-related MDS, secondary AML. You see both molecular and cytogenetic abnormalities that are most common. And, again, *TP53* is right up there at the top. The other thing I say is seven is not lucky in MDS, right? Anything that's a minus seven in MDS, those people tend to convert to AML much more frequently than people who do not have that abnormality. But you can see here, again, we have common players here. *FLT3, TP53* are right there up at the top.

So what are we going to do for these people? Well, this is a disease that you do not watch and wait, right? So, generally, treatment is immediate. The struggle that we face right now is that, you know, we need all this information and

it matters and you want to get the diagnosis right, and doing that morphologically by itself now is really not enough. And cytogenetics, even in the best of situations, usually take about a week. Some of these molecular studies if they're send-outs can be 10 or 14 days, so it's really our challenge to do these in an expedited way.

There was a study 7 years ago, Dr. Nickel Securus and others, that looked at elderly AML and found that really you could wait at least a week or more and it didn't really change the outcome for those patients. So there's nothing wrong in the older population in particular. If you're really worried about an antecedent hematologic malignancy or one of these other subtypes to give it some time and supportive care, get lines put in, and do all the diagnostics, use hydroxyurea if you need to control their blasts. So you get the right information before you actually decide on treatment. The big question always is are you eligible for transplant? And sometimes that becomes really the determining factor in how aggressive we are up front.

Induction therapy is still our primary goal; we want to suppress that marrow, clean it out; hopefully, then what grows back is healthy. We're going to do consolidation because even if we do a day 14 marrow and there's no evidence of disease, we know that at a molecular level, those cells are going to be there. And so, we are now moving into an MRD-negativity phase with AML, much like we are in other hematological malignancies where you're saying at a molecular level "I cannot see any abnormalities." That's something that's really

being pushed and really being part of what we decide on whether somebody can actually go to transplant.

The last thing you want to do is take someone to transplant with active disease. They just don't do as well and they're really much more at risk for a relapse. So, then we say, "Okay, if the end game is really an allogeneic stem cell transplant…" This is work that has primarily come out of Washington, and I know Gabe has a couple slides, as well, on the case. But the deal is here to really look at all the organ systems and say are they up to snuff or not? Are they otherwise healthy or not?

You can see a whole list where you get a score of one here and then you get down into a score of three. So, prior solid tumor, heart valve disease, heart valve disease, severe pulmonary disease, or moderate or severe hepatic disease gets you a score of three all by itself. So when you think about that, then they said, "Okay, that's fine, now this is evolving." Originally that work was done in 2007.

And then, they started to say, "You know, let's look at age. Does that matter?" Well, we saw the age curves, and so they said, "Let's do this composite score where we add age and then we're going to add in cytogenetic factors and we're going to categorize them as favorable, intermediate, or adverse." And you saw that list. So now they're saying, "All right, we're going to account for more of the disease attributes; we're going to add age; we're going to look at organ function collectively, and how does that look?" So if you see here, this composite score of greater than three, it's associated with inferior outcomes. You can get

that simply by having valvular heart disease or you can get it because you are of an older age and you have adverse cytogenetic abnormalities.

So the way you get to that score might be different, but either way it's unfavorable. It's becoming more and more precise in really estimating risk and making a proper decision about how aggressive should we really be with the individual patient?

And then, this is just looking at adding that, again, altogether in a different way where you're adding the age score in to the composite score and then, so you're getting up to a score of five by doing that. And you can see the differences that that makes. So really, a new way of looking at things.

And then, they said, "Okay, well, that's all great. So, now we want more." Now we're going to say if they present with a low albumin, what does that—that's always worrisome for me. People that have been in the hospital for 21 days and their albumin is 1.9; that's never good. I worry about those people; they are not going to do well. It's going to be really hard to treat them again. Their platelet count being low, their LDH level being high, and so they've added that into the factor, and then, ultimately, come up with this total composite score with all of those other items and look at how those break out. It's really becoming an art to assess risk. It's no longer just cytogenetics, it's no longer just age, it's all of this together: organ function, comorbidities. And we need to do this work to really do the right thing for the patients and not over-treat and not undertreat.

So with all of that, and you finally get through that, you're like, "Woo, that was a lot of work." And then we're going to say, "Okay, if you're medically fit and

you don't have one of those higher scores and we want to do induction, the standard of care is still 7+3." But one of the first questions we're going to ask is, "Are you *FLT3* positive or not, mutated or unmutated?" That's going to make a difference in whether we add something to induction with 7+3, specifically midostaurin, at this point. And, ultimately, our end game is still are you eligible for a transplant? Because most standard therapy other than core-binding factor AML is not curative with the exception of APL in some cases, which is really treated in an entirely different way.

If they're not *FLT3* positive, then you're going to really go back and say, "How fit are they?" You know, there's levels of fitness and what can they handle? If they have secondary AML, you're going to think about using the liposomal CPX-351 or daunorubicin and cytarabine for their induction. And in some of the elderly AML where they're marginally robust, then you may treat them with a hypomethylating agent similar to what you would do for MDS.

Standard of care is still 7+3. We still do the day 14 marrow, we want it to be empty and their counts aren't bottomed out. We get sad because we don't think it's working. We're going to say if they have residual disease or not. If they have residual disease, they need reinduction. If they then are negative, we're going to do a recovery marrow and hope that all those cells are healthy and there's no residual disease then.

If they fail two inductions, that's really bad news; salvage therapy is marginally beneficial in these patients. I think what we are seeing now is there are people—we had a conversation with somebody that said they're beginning to

not even do the day 14 marrow because what's it going to do for you, right? It's become a habit for us. And, ultimately, what you want to know is when the marrow recovers, is there leukemia there? And you're going to know whether they bottomed out their counts or not. There are people that are getting away from this day 14 marrow, which is probably good for patients, just to know that.

If they're medically unfit, then we really need to say, "What's the tempo of that disease?" If they've got 76% blasts and it's climbing, that's one scenario. There's those people that are just tiptoeing along; their blasts are just pretty stable and they're not really that aggressive. That's going to mean something different, and that's where we may use something like azacitidine. Or always in these patients, we want to consider a clinical trial.

7+3 has been around for eternity; 44 years later we're still doing it. This is 1973 Yates and colleagues. It's still the standard of care for patients with newly diagnosed acute myeloid leukemia. We have many of these trials. As you saw some of the examples in the algorithm, they're adding something else to that to optimize these other targets that are being identified as prognostic indicators. There are the patients who do well with this low-intensity treatment, so even azacitidine. Azacitidine is actually the only drug that has survival data. Many people will argue that the trial designed for the decitabine was just not done well, and so, there are people that prefer one or the other. There's still people that use low-dose cytarabine. My experience has been it lowers their counts, but then they just become pancytopenic and you're not really adequately controlling the

leukemia. There are instances where we just give that supportive care and we control the blasts with hydroxyurea and maybe transfusion support.

Let's talk briefly—and I know you've heard some about these drugs, so I'm just going to touch just on some of the points that maybe we didn't cover. This is just a list of all those, and you can see that they have different mechanisms of action. We have the *FLT3* inhibitors, some off-target affect to c-Kit; PDGFR, which is platelet-derived growth factor VEGF actually—and marrow's a very vascular place and VEGF plays a really big role in the balance of apoptosis program, so death and depression of disease. When people are progressing, that apoptosis program is not working and progression takes over. A lot of that has to do with VEGF.

We mentioned the *IDH2* mutation and the IDH2 inhibitor and axitinib or AG-221. Venetoclax not approved, but there are trials going on. And then, we're going to talk about a couple of the other drugs.

So, you heard about the purple drug, like this daunorubicin. And, actually, why it's purple is there's a copper compound in there and you combine that copper compound—there's little dots in there—with some of the lipid structure and it creates this very deep purple color. So, it's now forever more the Barney induction, according to Dr. Harvey. But it's a very purple drug.

And there are different dosing regimens than 7+3, but it's still a combination of daunorubicin and cytarabine, so the toxicity profile, the things that we are worried about in 7+3; cardiac function, vesicant, still apply. Even though it's compounding in a different way, the drugs are essentially the same, they're

just in this different molecule. So, you have to treat it with the same respect and safety, and I'll skip over that.

Here's the trial design—which I think you also saw earlier—randomizing to a standard 7+3 or the CPX-351. And you can see that it's dosed in induction days 1, 3, and 5. And then, in cycle 2 just days 1 and 3. So, consolidation, which is very different in standard 7+3 when you get 3 days of daunorubicin and you get 7 days of continuous infusion of cytarabine.

These are the outcomes, and you saw those survival curves that were presented earlier, so there was an overall survival advantage in the patients getting the liposomal compound. And this is basically that survival curve favoring the patients doing liposomal versus standard 7+3, which is in that golden rod color. It did make a difference for these patients. And the majority of these people were older and had this high-risk AML, which either had antecedent hematologic malignancies, specifically MDS, or treatment-related AML. So this is pretty impressive in that high-risk group, which don't really do well with standard therapy historically.

Again, in the side effect profile, very much the same. The one thing I would mention that Dr. Harvey didn't mention and that's different: our paradigm has always been day 14, day 28, right? And treat as soon as the count's recovered with consolidation. It's keep the intensity—go, go, go. What you do find in this drug are these prolonged cytopenias and particularly platelets where it may take you 7 or 8 weeks for that patient to recover. If you go back and you say, "Okay, you know what? They actually did better with overall survival."

And a slide I don't have on here is a greater depth of response, so there were more CRs. Then, you can say to yourself, you know what? We have to think of this in a different way and move away from the standard paradigm of day 14, day 28 because we may not be able to retreat them until week 7 or 8. And that makes people freak out because we're so used to this 14 and 28 that we've been doing for 44 years. So we have to rethink our paradigm in a lot of these new drugs.

These prolonged cytopenias can mean that you can't do consolidation at the standard day 28. And that's okay with that drug because that's how it behaves. It's like a somal; it stays in there. It gets into the marrow space more efficiently because of how it works and it exposes those cells over a longer period of time.

Now, here's *FLT3*. I made this slide in whatever, 2004? And so *FLT3*. A cell surface tyrosine kinase protein commonly mutated in leukemia, which is associated with leukemogenesis. Basically, as you heard, it's constitutively on; the gas pedal's to the floor all the time making these abnormal cells. And it's associated with a poor prognosis, so that would be the right answer.

This is the RATIFY trial; we heard a little bit about this. This is midostaurin, a FLT3 inhibitor, added to 7+3 in newly diagnosed AML. It is not intended as a single agent and it is intended to be given with 7+3. And you can see that there was a statistically significant difference for your overall survival and increased repeat responses.

Adverse events: not surprising anemia, but there were some rashes and some with dusk formation in the midostaurin arm compared to the placebo arm. And nausea was pretty equivalent across the two groups.

This is a newer FLT3 inhibitor not yet approved, gilteritinib. It's highly selective, potent FLT3 and AXL inhibitor. This CHRYSALIS trial was a phase I/II study, so 252 patients, which is a pretty good number for AML. Primary endpoints: safety and tolerability and pharmacokinetics/pharmacodynamics; that's what PK and PD mean. And they found that the drug is taken up and has benefit. They do have seven deaths on this trial, so it is something that's being moved forward, but carefully.

Then this, again, is showing the difference in the outcome in overall survival in the patients receiving that drug. And, again, looking at dose finding for what's going to be the appropriate dose to move forward with the phase III trials.

We talked about *IDH2* in AML, so *IDH2* or isocitrate dehydrogenase. This is part of your Krebs cycle. You're like, "Oh, my God, don't make me do the Krebs cycle; not now!" But it has a lot to do with how cells develop normally or don't. And what ends up happening in the presence of mutation is you get this methylation, and we know that hypermethylation is leukemogenic. We also know that there's impaired cellular differentiation, and what that means is cells don't grow up normally; they can't mature and do the things that they're intended to do.

Itacitinib we've heard about, again, a couple times yesterday and then again today; it's a selective oral IDH2 inhibitor first in class. And we do need to

know—and this is why it's so important when you're first diagnosing a patient—to be sure that you're answering all the questions.

The other thing that's really important is that this drug is approved in relapse disease. The disease you start with is not the disease you'll end up with, right? So, you may have been *IDH2*-negative initially, but you can acquire mutations in some cases, and so we really want to be able to answer that question at each point of analysis, so it works by inducing differentiation. As a part of that process when cells are differentiating and developing, you can actually see what looks to be like an increase in those cells before it actually begins to look better.

And this is another paradigm shift, right? We're used to seeing all those numbers go down and bottom out. And when that doesn't do it and it's AML, we get a little uncertain. So, you have to understand the mechanism of action. What is that drug doing in the system? What do we expect it to do? And stick with it long enough to actually have the opportunity for benefit.

So you're really changing the dynamics of the disease by giving that treatment, and that's going to take a little bit of time. Several months of treatment may be required and you want to continue the daily itacitinib. It's generally well tolerated in the study.

Here's the data from the phase I/II study of itacitinib; really pretty well tolerated. Some diarrhea and fatigue, but most of these were mild or moderate in severity. Vomiting could be well managed. Other serious related adverse events were rare, but there is this phenomenon called the differentiation syndrome. And

you saw the examples that Dr. Harvey showed and that Dr. Artz showed, but basically if you've ever treated somebody for APL, it's the same kind of thing; they have this flurry of maturing cells that can cause fevers, chills, pulmonary infiltrates, shortness of breath that can be very effectively treated with steroids; if in doubt, give steroids. And it generally passes with time as you moved past that initial differentiation. Really important to keep an eye on that and the trajectory, again, of the disease that can take several weeks to see benefit.

In the studies, permanent withdrawal of the drug was not required, so people worked through it. They didn't stop the drug unless there was something very severe going on. And you can see the CRs with incomplete hematological recovery was 28% in this group of relapsed patients, high-risk treatment-related, and higher risk patients just by virtue of having relapsed. They received 100 mg a day, and the median time to first or best response was 1.9 to 3.7 months—so way, way, way beyond the 14 and 28 days, right? So you just forget about it and no more. Fourteen and 28 does not apply in this situation. We need to look at it in a different way.

This is just showing that evolution of best response, so it takes time. Also very important to keep in mind, you can see that the depth of response actually improved over time. This is just getting back to some of that safety information. We talked about the differentiation syndrome. Most of these were not of higher grade. They were mostly minor or grade 1/2 as opposed to grade 3/4, but there were some grade 3, which is what's represented here. Keeping in mind differentiation syndrome, all the things that come with treatment of leukemia,

which are cytopenias; not a surprise. Fatigue, also. And then, there were some cases of increase lipase levels.

Gemtuzumab ozogamicin. How many of you guys used that the first time around, right? So we're dating ourselves. The problem there is they have dosing that led to some problems with people in terms of infectious complications in particular, and then their endpoints were not met in these trials. And so it got shelved and then got brought back with different dosing parameters and actually has now been approved in three different indications—which I don't have all on this slide here—but, basically, came back and now was approved very recently—September 1st—with lower recommended dosing.

The other drug that came about and everyone was really excited about this—this was another anti-CD33 drug—dacetuzumab. Really looked exciting and the data looked very exciting. And, unfortunately, they had to withdraw this drug from the market due to patient deaths. And so, this happens in trials where people see deaths and the drug doesn't get to move forward.

The other drug, vosaroxin, is a first-in-class anticancer quinolone derivative, so a very novel compound. This is something that interplays DNA and inhibits the topo II and basically not a P-gp substrate. So your p-glycoprotein is something that basically allows the drugs to be pumped out of the cells so that you can't get them in there to affect the DNA. So it's important when that's not an issue, a p53-independent activity. And so, this is being looked at in this VALOR trial and translated to prolong survival in relapse/refractory AML, particularly in older patients, so we'll see how that goes.

Bcl-2, which is a very unique mitochondrial point of activity in AML, venetoclax, which we're already using in other disease states. This is a highly selective orally bioavailable BH3 mimetic, so basically, that's that particular pathway. The Bcl-2 proteins are very critical to apoptosis, and Bcl-2 is overexpressed in AML, so it makes that a very attractive target. This was a phase II study looking at 800 mg a day; this is higher than what we use in CLL. Overall response of 19% as a single agent, so showing some activity.

Interestingly, *IDH1* and 2 mutations were present in 38% of those patients, and that becomes an interesting though. And toxicity profile pretty manageable.

This is now looking at now that we have these drugs where we can attract these novel targets? It makes sense to start to combine them, right? So you're coming at things from different angles, so much like adding the FLT3 inhibitor to 7+3. How can we exploit different targets at the same time? This is a phase IB study, so a very early study; venetoclax plus a hypomethylating agent in patients with newly diagnosed AML over the age of 65. And 34 patients in this study, median age of 73, adverse risk in a big number of 41%. And they're treated with venetoclax 400 or 800 with either decitabine or azacitidine and CR plus a CRi of 71%. So, looking, honestly, how some of these people may have responded to the hypomethylater alone; but, again, an interesting combination.

Where are we are going from here? Well, we're going to look at all these molecular profiles. We're going to have to live and breathe all this; this is the way forward. Looking at protein kinase inhibitors, epigenetic modulators, mitochondrial inhibitors, such as the Bcl-2 inhibitors; many other things that are

being evaluated. And then how are we going to combine all of these as we move forward? It's an exciting time; there's a lot of good work happening. We're going to see more and more of these things moving forward. And I'm going to turn it over to you.

GABRIELLE All right. Thank you, Sandy; that was an incredible amount of information.

I'm going to go through a couple of case studies in AML to try to put in a little real-life context. Our first case is a 36-year-old gentleman who was diagnosed with AML in July of 2016. He actually presented with a very high white count of 84,000. He was mildly anemic, mildly thrombocytopenic, but he had 30% circulating blasts. He was *NPM1* positive, *FLT3* negative, and *IDH2* positive. His cytogenetics were notable for deletion 16q. He had good cardiac function, and his exam was really unremarkable.

His toxicities included pancytopenia and transfusion dependence, which you would expect from his G-CLAM and consolidation. He went on to get a second consolidate—the pancytopenia in our center is classified ANC of less than 500, at which point they go on Levaquin and posaconazole. They get acyclovir throughout their induction and consolidation.

He also had mucositis and neutropenic fever, which for us, again, less than 500 and a temp greater than 38.3 always get admitted. This poor gentleman was bacteremic with a MDR E. coli, and he was actually septic.

I'm going to take a break from the AML piece of this and just talk about some of the side effects that we deal with. I'm sure you've all heard of the

surviving sepsis campaign; there's a website there that you can look at for a little bit more detail. But we really want to use the good tools that we have. qSOFA is probably by far the best screening tool that we have, and that includes an altered mental status, tachypnea with a respiratory rate of greater than 22, and hypotension with a systolic less than 100. Some people do like to use SIRS, but all it takes is your neutropenic patient to have a fever and they already have met the SIRS criteria.

The other soft indicators are do they look toxic? What does the family think? Usually they have caregivers that are coming in with them and say, "Joe just doesn't look right," or "We can't get him off the couch," et cetera. What are you going to do? Labs; you want to get blood cultures, two please: one from the line, one peripheral. Get a urine culture and a chest x-ray if you can. Venous lactate is really helpful for following the trajectory. If they're hypotensive, you want to give them fluid bolus. And when I say fluid bolus, I mean 30 mL per kilo per hour; that's two liters for a 70 kg individual. The lactate should also be followed just to make sure that they're responding to what you're doing.

Antibiotics within 3 hours is the goal set by the surviving sepsis campaign. Ideally, the sooner you get him in—preferably an hour—the better. You want to make sure that you're reassessing your vitals and fluids on a regular basis. This is the 2006 study from the Critical Care Medicine. It is retrospective, but it's 2,000 patients that showed a marked survival advantage if antibiotics were given in less than an hour or an hour or less; 80%, which is pretty amazing.

Back to our gentleman. He finally got out of the ICU, got discharged. His marrow showed no evidence of disease. His previously noted *NPM1* positivity had gone away, as had his cytogenetic abnormalities. He got admitted for HiDAC and, unfortunately, on day 22 presented with circulating blasts. So he gets cytarabine and decitabine, to which he did not respond. And he was started on intermediate dose of cytarabine with itacitinib started on day 17; he tolerated this actually pretty well. He had quite a bit of nausea, but as you know, we have some great treatments to address this.

He was not eating, which was really problematic for this guy because he's only 36. But he actually did really well on this therapy. I don't know exactly where he is in his therapy today, but he did really well. This is a great example of using this particular drug in a relapse/refractory setting.

Our next case is a 72-year-old gentleman who presented to a community hospital. He had progressive fatigue that had been present for quite a while. He had previously been very active—golfer—but had gotten more and more fatigued to the point where he wasn't able to carry on his usual activities. He hadn't seen a medical provider for 16 years and was taking no medications.

So when he was first seen in the outside ER, he was febrile to 38.5, he had flu-like symptoms, and profound fatigue. His labs were notable for a creatinine that was slightly elevated at 1.35. His LDH was markedly elevated at 629; upper limit of normal is 180. His albumin was slightly decreased at 3.1, INR was 1.26. He had 161,000 white cells, profoundly anemic, and thrombocytopenic, and had a high amount of circulating blasts. So he was admitted to the hospital

for IV antibiotics. He got hydroxyurea and fluids while his workup was completed. He really did not want to be in the hospital. Fortunately, we were able to support him on an outpatient basis with regard to his transfusions while we were completing his workup.

His past medical history is actually notable for Hodgkin's disease; he got ABVD and radiation. And, essentially, after he completed that therapy, that's when he decided he wasn't going to have anything to do with medical people. What are we worried about here with a white count of 161,000? Yep, tumor lysis syndrome.

There's a lot of risk factors we can look at; the tumor type. Burkitt lymphoma is a very high-grade lymphoma, and, obviously, that's going to be very high risk for tumor lysis, their tumor burden. Elevated LDH; you'll notice that's more than two times the upper limit of normal. Elevated white count greater than 25,000, renal function, and a baseline uric acid. So stratification by risk, this gentleman had AML. White count was really very high; he also had a high LDH, so he had a pretty good risk for tumor lysis. Fortunately, we were able to get a lot of these factors corrected by the time he got discharged to the outpatient setting.

In terms of managing tumor lysis syndrome, you don't want to be in a position where you're having to follow those items on the left-hand side. You want to be very aggressive in your hydration; you can use sodium bicarb if that's appropriate. You want to have them starting on allopurinol immediately and, in severe cases, rasburicase; very expensive, but very effective.

Going back to our gentleman; the rest of his workup showed an LV function of 52%, so on the low side, but okay. His marrow showed, not surprisingly, 90% blasts, he was *NPM1* positive and *FLT3* negative. His cytogenetics were notable for deletion 5q and trisomy 8. So, in all likelihood, he had MDS probably for a while that was related to his treatment with ABVD.

I'm just going to take a minute to talk about treatment-related mortalities, treatment mortality index. On the top line here, you can see there is about 12 or 13 factors that help us identify people who are at high risk for dying within the first 28 days with standard of care. You can see on the lower right side there 0% chance of survival. Seventy-two-year-old treatment-related MDS that had progressed to AML.

We're trying to think out of the box about what we could do for this gentleman. And he was actually enrolled in the CPX-351 trial. He got induction therapy in an outpatient setting, mostly because he refused to be admitted, and he did really well. He had no problems with the infusion itself. He was able to come because his family, his son actually, came up from California and was his primary caregiver, so he was coming back to our center on a 3-to-5 days a week basis.

So, toxicities. Sandy talked a little bit about prolonged cytopenias, and he had a little bit of that; it really wasn't too bad for him. We'll talk a little bit about transfusion dependence; most of our AML patients do get transfusion dependent. We use a platelet threshold of less than or equal to 10 or hematocrit of less than or equal to 25. Obviously, those things can be adapted if you have a patient that

has a recent bleeding history or cardiac issues where they just don't tolerate a lower hematocrit.

The other thing I want to just add to that is that if you have a patient that you think in any way is going to go to transplant, you need to make sure they're getting irradiated and CMV safe blood products.

Unfortunately for this guy, his day 28 marrow showed persistent disease with 40% blasts. He got re-induced with CPX-351. Again, in the outpatient setting. He tolerated it very well. He did get admitted with a neutropenic fever, transfusion dependence; the usual side effects of treatment. He had count recovery slightly delayed at day 36. His day 38 marrow was normal cellular by morphology, his flow was negative. He did have no abnormal blasts, but he was *NPM1* positive. So, he had two cycles of consolidation with CPX-351 that was completed in 2016 and then he was, of course, lost to follow-up because he didn't want to come back and see us. We've probably all had patients like that.

He really did well until June of 2017 when he finally called us and said, "I can't even get out of bed." He came in and he had relapsed disease with 42% blasts. But, I'll tell you, this gentleman that had a risk of treatment-related mortality with a 0% chance at 28 days, he got over a year out of this approach, so it was a pretty phenomenal response.

Our third case is a 62-year-old woman with a 3-year history of thrombocytopenia, which had progressed to pancytopenia. She presented with a white count of 49,000, a little bit anemic, thrombocytopenic; not terribly. She did have 76% circulating blasts. Her chemistries were pretty normal: creatinine 0.8,

LDH 224, slightly elevated, but not terrible. Uric acid was normal at 4.8, bone marrow showed 60% blasts. She had trisomy 8, *NPM1* positive, and *FLT3* positive. She was extremely anxious, but otherwise, she actually looked pretty good despite her anxiety.

Going back to something Sandy talked about with the European leukemia and that risk stratification, she is intermediate risk with a mutated *NPM1* and *FLT3* positivity. She got standard 7+3. She did really well with the infusion; no toxicity. She did not have any cerebellar issues. She was discharged on day 6.

At our center, we are fortunate enough to have great outpatient support, and our patients can qualify for early discharge, so they're not in the hospital for a month waiting for their counts to recover. Essentially, we use age less than 65; they have to be within 15, 20 minutes of the medical center, be willing to come in for three times a week labs and associated transfusions, and a caregiver with a patient.

She started on midostaurin on day 8, and she really did well. She tolerated the drugs and the treatment very well. She did get admitted with a cellulitis, but that resolved with IV antibiotics and she got discharged. Her day 28 marrow showed no evidence of AML. She got consolidation with HiDAC. Again, early discharge, did not have to get readmitted, and got started on the midostaurin again on days 8 through 21; usual toxicities of treatment. This lady actually arrived to our transplant service in October of AMS-unrelated donor transplant in first CR, so this is a good success story.

I'm going to touch upon the Stem Cell Transplant Comorbidity Index. This actually takes into account 17 systems of potential organ dysfunction and gives you a composite of how is this patient going to do in transplant? I will just leave you with the thought that you can look at all of these things—you want to factor them into your decision making—but nothing's going to take place of a transplant consult because they're going to look at what are the condition regimens that patient might get? What are the donors? Do they have a match sibling? Do they have an unrelated donor or a Haplo-Cord? There's a lot of factors that go into this, aside from the comorbidity index.

In summary: lots of tools out there; please use them because it really could help direct your therapy and into better outcomes for your patients. We have a lot of targeted therapies that are now available and they're a wonderful addition to therapy. They're very well tolerated in the experiences that we've had in our center. And keep the toxicities in mind; plan for your patients to get transfusions; look out for tumor lysis syndrome, since this is a big player and there's a lot of work out in the community trying to decrease morbidity and mortality associated with sepsis. And then, finally, differentiation syndrome is something to keep an eye out for in certain classes of drugs. All right, everybody got all that committed to memory?

SANDY Any questions; anybody have any questions? There's somebody; just two of them.

FEMALE Yes. How long after you start treatment with the itacitinib would you expect to look for symptoms of differentiation syndrome?

SANDY The onset can be anywhere from a few weeks to several weeks, so really you want to be really keeping an eye on people as early as 2 weeks out, 10 days to 14 days out and then, up and through—really keeping an eye on people. During that time of response is when you're going to see it. So, even though the time to response was 1.9 to 3.7 months, you can actually see the differentiation syndrome starting a little ahead of that. So really being astute to those symptoms throughout that period of time because that's where you're seeing the differentiation. There was somebody else that had a question over here.

FEMALE —because I understand there might be an algorithm that you were thinking or developing? One of the people I work with are, you know, we're all groupies for you, but just to differentiate to infection.

SANDY We were just talking about having kind of a roadmap about, how does that look time to onset? What kind of things might you see? It can be a little misleading because we're in this paradigm of expecting all the numbers to drop and be zero, right? And, instead, what you're seeing is actually things going up. And when you're looking at the leukemic blasts—they're generally of the neutrophil lineage—that myeloid lineage that's going up and so, you're worried because it's going up instead of down or you're not seeing it go down and then they can develop those secondary symptoms.

So, it can be a little misleading to people and this is why you have to say, "Okay, you know what? I'm using this drug and this is what I'm expecting." And you can use an analogy to people that are going to ibrutinib for CLL where the

number's actually going up because of the change in the migration of the cells out of the nodal region into there peripheral blood, so it's a totally different shift, and it's based on the mechanism of action of the drug.

If we think about how the drug works, it's a differentiating agent. Cells are going to mature and develop and grow where normally they've been blunted because of the leukemic clone. Then you're going to see the numbers go up or not go down, which you would normally expect to see in standard therapy. It's just a totally different way of setting expectations really. Do you have something to add to that, Gabe?

SANDY Over there.

FEMALE (Inaudible)

SANDY Steroids.

FEMALE Antibiotics, too?

SANDY No, they're just steroids usually.

FEMALE Yeah.

SANDY When you think about what's differentiating, right? These are the cytokines that come with that differentiation, that development, of those cells are what are producing these symptoms, so, basically, it's steroids. In some cases, if they have fluid that comes with that, you give diuretics, but it's the same thing you would do to treat differentiation syndrome in APL.

GABRIELLE And it depends where they are in treatment because there are times if they're neutropenic and you don't know exactly what's causing their fever—

FEMALE That's why I was asking because sometimes I understand that there can be like maybe mild dyspnea on presentation and maybe a little bit of hypoxia versus—so, it just seems like a complex—

GABRIELLE You probably want to do more than one thing at a time and then peel back one at a time your therapy, so once you figure out exactly what's causing the problem.

SANDY Yeah. You have to actually do the clinical workup. This is why you need the baseline chest x-ray, or if that doesn't answer it, get a CT of the chest. But if you're really worried about differentiation, then steroids are really going to take care of it, yeah.

FEMALE Thank you.

SANDY Anybody else? All right, don't forget to claim your credits and complete your evaluations, please. Thank you for sticking out this long day and have a wonderful night's sleep or a wonderful time with your nightcap, whichever you choose. And, hopefully, we'll see you tomorrow for our closing program. Have a good evening; thank you.

[END]