Managing the Continuum of Myeloid Malignancies (CML, MPN, MDS, and AML)

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MS. KURTIN Welcome back, everyone. I hope you enjoyed the keynote presentation and the posters and had a nice break. I'm Sandy Kurtin, and I'm a nurse practitioner at the University of Arizona Cancer Center in Tucson, Arizona, and a founding board member of APSHO, which I'm very proud about and pleased to introduce this next session. Our final presentation of the day in this room is "Managing the Continuum of Myeloid Malignancies." There's been 25 years of nothing and suddenly we have a lot of new things happening, so it's a very exciting time, and our presentation today is going to be provided by Dr. Andrew Artz and Jean Ridgeway, a good friend and colleague, both of them from the University of Chicago. So Dr. Artz or Jean.

DR. RIDGEWAY I'm Jean Ridgeway. This is my good friend and colleague, Dr. Artz, and we're going to talk to you about a very big topic in a very short amount of time. Our learning objectives. We are going to talk about the WHO criteria, disease definitions for diagnosing these myeloid malignancies, and we're going to talk about the JAK-STAT pathway and then recall the mechanism of action for some of the new novel therapies for AML. Then we are going to also look at the clinical relevance of molecular mutations including FLT3 and the IDH mutation. We are going to talk a bit about germline mutations in patients with predispositions for myeloid malignancies, and then our topic—very favorite and near and dear to our hearts—at the end we are going to talk about safe and

current treatments for older patients with myeloid malignancies. These are our disclosures.

DR. ARNTZ We are going to discuss the 2016 WHO disease classification for diagnosing myeloid malignancies and talk a little bit about germline mutations, discuss the clinical relevance of molecular mutations in AML including FLT3 and IDH2, a bit about myeloproliferative neoplasms and the JAK-STAT pathway, some novel therapies for these and their mechanism of action, and then we are going to build a little bit on what we discussed and how you can do this as a collaborative team, which is where we work primarily together in that allogeneic transplant setting for myeloid malignancies, especially for older adults, and talk about our transplant team and our work together as an interdisciplinary model. First, to discuss the latest WHO disease definitions for diagnosing myeloid malignancies. This is a very dense, dense topic. But as a clinician, we can summarize what are some of the key points for people who manage patients without having to go through all of the slides and morphology. And if there's one key point in the 2016 revision of the classification, the textbook of how we diagnose them, it's really that we've entered the genetic era in the actual classification, and you'll see that scattered throughout the talk. That's really a key thing as far as the myeloid malignancies go.

Because a lot of this is related to genetics, I want to give you what I consider just a very simple primer, and I apologize if it's too simplistic, but when I think about the genetic changes in malignancy and especially blood cancers, this is one way to frame it. If we think about a category, there are different types of

mutations. There's translocations; here we can think about the BCR-ABL, 922, Philadelphia chromosome, a JAK2 mutation, or a TP53 might be some examples of genetic changes detected by different methods and they can help you in different ways. Diagnostically it can be essential, so CML, as Jean will talk about, requires you to find this translocation or the 922, and in ALL, it will put you in a certain group or category in the Philadelphia chromosome group. If you think about JAK2 mutations, its present variably in myeloproliferative neoplasms so it helps but isn't required for diagnosis, and the TP53 isn't necessary for diagnosis, but it does suggest a neoplasm is present and it also suggests a potential hereditary link in some patients. What about prognosis? Genetic findings can also help you prognostically tell us what the future might hold, so in the Philadelphia chromosome in ALL, for example, confers the worst prognosis at least prior to the tyrosine kinase era. JAK2 has been varied in its prognosis, and TP53 has usually been worse. Just some examples of how it helps us prognosticate. And what about predictive? So these genetic changes can also be predictive biomarkers. What does that mean? It either enriches for response to tell you what someone might respond to or not respond to and/or it can be targetable. Those two are separate, but they can be linked. For example, the Philadelphia chromosome, we know that the tyrosine kinase inhibitors, imatinib, dasatinib, nilotinib, etc., actually target the defect and can be used to obviate the adverse outcome. The JAK2, it's a little less variable. You can even use JAK2 inhibitors in people without a JAK2 mutation sometimes with benefit. And TP53, we don't have something targeted for it, but certainly it tells you that

cytoreductive standard chemotherapy often doesn't work well in a lot of diseases that harbor a TP53, but other treatments such as decitabine in AML or ibrutinib in CLL with these TP53 can be useful.

I wanted to show you Janet Rowley is someone who worked at the University of Chicago and both of us knew her and she really helped introduce us to the genetic era and was seminal in the discovery of the BCR-ABL. The first introduction to the WHO and one of the major changes is this provisional classification of family, familial or hereditary if you will, myeloid malignancy syndromes. How many people have heard of that? Just raise your hands if that's familiar to anyone just so I get a sense. Okay. So they really fall into three different categories, and what's really important to know is that you as the providers, APPs, etc., you need to get a lot of this from the history, and a lot of times the classification will not be done properly if you don't ascertain the information. What I mean is that patients who have AML with this mutated CEBP alpha, if it's inherited they get classified differently than if it's a germline predisposition, but someone has to know enough to think to test for it. And they are divided into three different groups: people who have hematologic malignancies alone with this germline predisposition mutation, platelet dysfunction, or other organ systems affected. So for some of them, in the WHO, we see a familial AML with mutated CEBP alpha; you see them listed here. DDX1 is a recently discovered mutation. Some heme malignancies are inherited; there are families where they have multiple family members with blood cancers and myeloid malignancies. It's not necessarily a coincidence. There's another

group that has platelet dysfunction, so the patients may have low platelets and a bleeding diathesis perhaps more than the low platelet count would suggest. Maybe the platelets are 90, but they are having a lot of epistaxis and a history of significant bleeding and that's a different set of mutations that predispose to these conditions. And again, this is the history that if you hear it from the patient, you need to be alerted and aware, put it on your bone marrow requisition and let the team know so that they can consider subsequent tests and subsequent step. Some of these have additional organ systems affected, and I'll show you on the slide after this where things outside of the bone marrow are affected because of the mutations or changes.

This is the actual WHO table of little dents as I promised, so we'll go by that. These are some of the other organs that can be affected. Things that actually we ask in our clinic every day when we see someone with AML or MDS or suspect it, we ask "Do you have any of these: early gray hair, head and neck cancer, deafness, skin pigment changes, pulmonary fibrosis, liver cirrhosis?" Some of these would be developed on the history, but most of the time, if it's there, no one would have put a link between the two. So how to identify, test, and manage adults with here it says "H" for hereditary instead of familial myeloid malignancy syndromes, and I thank Jane Churpek for the slide. Essentially, there are two main areas for you to focus on. If you see someone who is suspected or has MDS, AML, or aplastic anemia and empty marrow, we inquire about a family history of members with myeloid malignancy, a family history of multiple cancers especially in an individual, and we look for other organ systems involved as I

showed you on the last slide. Another way that people come to attention—and this is going to happen more and more in the future—is that there are panels of mutations as we all know, and more and more when you are testing someone you are going to order a panel, and it's going to have a lot of genes on it and they can range from a few to hundreds and some of those genes can be acquired mutations or hereditary, that is, you can't tell when you get the result back, for example RUNX1, if they say there's a RUNX1 mutation, say oh, that's just something in the leukemia cells; it might actually be in the germline tissue too and you would have to do additional testing. So you need to be aware of which mutations on that panel should alert you that maybe this could be a germline case, maybe this RUNX1, CEBP alpha, or other mutations are actually a problem. The reports might bury it; if you read the report it might be in there, but it will be buried, and then you need to do additional testing to know if it's germline.

You basically have to test tissue that's not the involved tissue, such as skin or buccal mucosa for example, and they have to do a specific panel for it. Another area that I think is always a struggle is diagnosing myelofibrosis, so PMF is primary myelofibrosis. And not that everyone memorized the last set of criteria for primary myelofibrosis, but some things that I want to highlight is that like all of the prior renditions of WHO, the first is presence of how it looks under the microscope, the megakaryocytes, the precursors to platelets, and they have to look abnormal as a major criteria, but also you can't meet criteria for some of the other myeloproliferative diseases. CML would be excluded by looking for the

Philadelphia chromosome, but this last one you can see the importance of genetic mutations. It's now a major criteria that we expect to see. There are JAK2, a calreticulin, or MPL mutation, perhaps another clonal marker in someone with overt myelofibrosis. If not, we are very suspicious that it may not be myelofibrosis. There is a caveat that you can still diagnose them, so it once again speaks to the importance of the genetic data in completing classification; it's not just about what it looks like under the microscope anymore. There are a few other rare entities of importance, rare myeloid neoplasms with established targets.

If someone has what you think might be a myeloid or a lymphoid blood condition, hematologic malignancy, and you see eosinophilia, these are some conditions that have to be considered, and some of them aren't picked up on routine cytogenetics, you actually have to order a specific FISH panel for them, and it's really important because they are targetable. PDGFR alpha and I should have said beta, they can be targeted by imatinib with great success, and you could have a great success with treating someone if you find this, and ruxolitinib may help for this provisional entity PCM1-JAK2. Again, the presence of eosinophilia should at least alert you to think about some other entities. MDS is always hard to diagnose for the pathologist and for the clinician because there are a lot of reasons why blood counts are low. Right? So when we think about MDS and classification, these are the five essential domains that are used in classification. The dysplastic lineages, erythroid, myeloid, omega karyocytes, the depth or the presence and depth of the cytopenias, low blood counts, presence

of ring sideroblasts, presence of blasts of course in the peripheral blood and the bone marrow are both important in this WHO, and the karyotype is needed. The genetic panels are required for diagnosis, but they help for refining prognosis. And if you look at the comments, there's some comments for each one, what's important. But I do want to point out for these that, generally speaking, you still, even in 2017, for almost all of these, there has to be some dysplasia in the bone marrow, so you can't diagnose MDS from the blood itself.

You can say there's probably a myeloid malignancy if there are blasts, but it really does require bone marrow for appropriate diagnosis and classification. Because there is sometimes a tendency to try to bypass that step, but it still really is essential. So I'm going to move by this one. I tried to shorten the MDS classification and the WHO into something more digestible, but it's still difficult. The way I look at it, I think a relatively simple way still that we have a high blast group and a low blast group. Let's start with the high blast group, essentially excess blasts. I do want to note one change from the last one where it was called refractory anemia in excess blasts, now it's just called excess blasts, so if you want to impress your doctors or someone else, tell them they're wrong and its now EB1 or EB2. Looking at the classification, if there are 5% or more blasts in the marrow or 2% more in the blood, it's at least excess blasts and there are no auer rods, but any auer rods, which are these abnormally shaped that they see in morphology, actually brings it up one stage or grade to EB2. You can see at the bottom 10 to 19% bone marrow, 5 to 19% in the blood of auer rods is excess blasts 2. And then all of the rest are what we call low blasts category, and they're

very difficult. Admittedly there are a lot of categories. What I want to mention though are a few different points here. One of them is that, again, you need the bone marrow test to really classify people. You will recall there's a deletion 5Q group, so if you have an abnormality of the deletion 5Q with only one other abnormality, that's its own group in the MDS classification, an MDS with a 5Q abnormalities, so it goes into its own group because it is sensitive to lenalidomide, so we like to separate those. And there's another group that's really important, it's the group with ring sideroblasts, which I should have probably shown you a picture here, but if there's 15% or more of those or 5% or more and again a mutation in the SF3B1—again it's a mutation you would find on a myeloid panel—then it falls into this group and they tend to have a more indolent prognosis. It's really important to identify them. It's also critical that you get a good sample because if you don't get a good sample, you are not going to be able to appropriately classify the patients and it's very hard to treat someone if they are not appropriately classified. Moving on.

This is AML. Your old AML has gotten much more complicated. It's AML and related myeloid leukemia in related neoplasms. The first thing going back to the theme of this about entering the genetic era is this first group of AML with recurrent genetic abnormalities, they call it provisional, but it will be there. These are the genetic abnormalities. Again, for the pathologists to classify the disease, they really now need the karyotype back and completed. They can say, "Oh, it's AML," but they really won't give you the full, the official, appropriate name unless they have all of this information. You can see if you look at the bottom of all of

these chromosome derangements that could occur, you see mutated NPM1 and biallelic CEBP alpha. This means that to appropriately classify someone in the present WHO, you actually have to test for these. And in some places, if you are not testing for them, you really can't get the appropriate classification for the patients. We have AML with myelodysplasia-related changes, which is generally adverse, meaning there's a lot of MDS-looking changes, but the blasts are 20% or greater. Therapy-related myeloid neoplasms just to recall although this hasn't changed, if you've had prior chemotherapy or radiation or an insult that causes MDS or AML, it's not AML by the classification system; we call it therapy-related myeloid neoplasms. You might say its therapy-related MDS or AML, but that's the official term, and we have to be able to inform our pathologists that there was prior chemotherapy or radiation so they can put it in the right category. Myeloid sarcoma is something outside of the bone marrow by itself, and we'll move past something for Down syndrome, I'll move by those.

We talked about the mutations and changes, and it has gotten more complicated,. This is a study looking at the, if you will, the portfolio of mutations that can be present. What's the mutational landscape in AML using our present technology? These are younger patients with AML, and you can see there's a tremendous spectrum of typical chromosome derangements and specific mutations that we find in patients. You can look with FLT3 and NPM2, DNMT3 being the most common, but look how many different mutations can be present across a large cohort of patients with AML. And now that we have all this information, we go back to the side of trying to think about how do we use that to

help us diagnose? I just showed you how NPM1 is a diagnostic category to help risk stratify, and Jean will go over in a bit how we can actually use them to be targeted in 2017. Some data on some of the most important mutations where we have the most robust data. NPM1, FLT3, ITD and CEBP alpha are really essential to test for. You can see in some studies of cytogenetically normal, normal karyotype younger adults with AML who received regular chemotherapy, if we look at their mutational profile just for these three, it widely separates outcome, and obviously that's really important. The NPM1 mutated has generally been thought of as a favorable group, although there's some of them that are unfavorable especially with a FLT3/ITD, if it's not mutated or wild type. CEBP alpha two mutations, we call that biallelic, is also favorable. And then if you have a FLT3 mutation, that's generally unfavorable, or you have none of these mutations, generally unfavorable. You can see for relapse-free and overall survival.

To make matters more complicated, it's not just the mutation, it's sometimes the burden of the mutation, so we call this the allelic ration, the mutant fraction. When you do some of these assays, some will just say "mutated," but more and more you are going to get a number that's going to say "20%, 30%, 50%" or "0.5" or "0.6." That's prognostically relevant. You can see in these studies of a lot of non-APL, meaning AML without 15;17 translocation, the outcomes of the FLT3 mutated ITD were very different and the worst were the lower curve, the 15% five-year survival for those who had a high mutant fraction. So that's become very important as well. And I think the most important tool to

risk stratify once someone has AML and you have your cytogenetics and your molecular features back is to use the European LeukemiaNet classification, which I'm listing here, but you can see again it incorporates both the cytogenetics and the mutations, and this group of adverse has grown and grown. This doesn't mean more people have adverse disease, but what it means is that we understand better because anyone who's treated AML says, "Oh, they were supposed to do well and they didn't." And more and more, we are going to do a better job of figuring out who was in a good-risk group or a poor-risk group so we can appropriately offer the treatments and treatment consolidation that best suits the disease. So IDH is another very important mutation, it's not an ELN, those classifications, isocitrate dehydrogenase and IDH2 is present in about 10 to 12% of AML and IDH1 in about 10%. I'm going to show you some data on the prognosis and Jean will talk about it, targeting.

We've talked about mutations being important, we've talked about allelic ratios being important, and now to make it even more complicated, some different types of mutations have different importance, and the concurrence of two mutations can alter the outcome. So for IDH2 by itself, it's not that meaningful, but if you have a DNMT3A and an IDH2 mutation, that's the green curve here, the bottom, so they do the worst and had the worst survival in this study. And then in other studies for people who have an IDH2 mutation at a different point, effecting a different nucleic acid the R172, they actually do poorly too. So this means more and more we're going to have to look at the reports and really look at the specific mutations. We've entered the genetic era for better or

for worse. I do want to make some commentary about collaborative practice since we do a lot of collaborative practice. The history though is really essential and no longer do you just submit a sample and they tell you what it is, you have to know the prior treatment, you have to know their family history for appropriate classification, it has to be on the bone marrow requisition for the pathologist to help you. If you don't say there wasn't prior therapy, they're going to call it not therapy-related and it's going to be incorrect.

You need to know what molecular testing is available at your center and figure out how you're going to interpret that data. Calibrating patient expectations is really important. It used to be we would do a bone marrow, we could tell you in two days, "You have AML, you don't." Now that we have to wait for the karyotype and all the molecular abnormalities often even to initiate treatment, we now have to tell our patients, "Look, we're not really going to know much for a few weeks until we get everything back," and that's very difficult for those of us in the room who have the patient in front of you. And then to understand the limitations of inadequate sample. If we don't do a good bone marrow and you're not drawing up the right sample you won't—a lot of these tests are unable to be performed. Now I'm going to turn it back to Jean.

DR. RIDGEWAY Okay. Thanks, Dr. Artz. I'm going to start talking to you about classic myeloproliferative neoplasms. When we think about MPNs, they are a proliferative neoplasm affecting the myeloid lineage, and you can classically think about two distinct entities: there's two distinct subtypes, those that are BCR-ABL positive, which would be our folks with CML and folks who

have BCR-negative myeloproliferative neoplasms. So these are the folks who have polycythemia, essential thrombocythemia, and then either primary myelofibrosis or post-ET or PV as well. What we've discovered over the years is that the JAK-STAT pathway is a critical pathway for our non-Ph-positive MPN patients. It's an intracellular pathway that's normally present, and what it does is it has ligands on the cell surface and these ligands send signals then down to the DNA. And it's necessary for growth and proliferation for a number of normal cellular functions for hematopoiesis, for erythropoiesis, for certain cytokines as well, and we what we found is that the JAK-STAT pathway is actually abnormal in a number of our MPNs, especially in MPN. And so when it's disrupted or it's dysregulated, it results in either immune deficiency syndromes or neoplasms because that pathway then becomes self-activated and it continues to proliferate, so we see our patients with PV or with really high hemoglobins or with myelofibrosis, these folks have definitely proliferative problems that are treated like a neoplasm.

What's happened in the treatment of JAK2 is that in 2011 we saw the first approval of a JAK2 inhibitor, a drug called ruxolitinib. Ruxolitinib, if you're not familiar with it, is an oral agent and it has a couple of approvals: one is for our patients with polycythemia vera who have failed hydroxyurea, or folks who have had advanced or intermediate and high-risk myelofibrosis. There are other indications for this drug, and it's under clinical development. It is an oral therapy, but it's not just selective for the JAK2 enzyme, and since it works within this myeloid system, when you look at the side effect profile, you expect

myelosuppression. Some other common toxicities with this drug if you've worked with myelofibrosis patients you know that they have a cluster of constitutional symptoms, and so the symptoms can be controlled with this drug. As a provider you need to know that when the patient comes off the drug, you need to do so slowly, otherwise they have a flare of those symptoms as well. And because of that as well we need to help our patients know that they need to be adherent and not just up the drug. On the other side of that algorithm our folks who have CML or chronic myelogenous leukemia, things have really changed in the past 17 years with the introduction of tyrosine kinase inhibitors. Before that, folks were treated not so happily with interferon or they were one of the largest cohorts of folks who got stem cell transplants. But now in 2017 we have a number of different therapies with tyrosine kinases, both in the frontline and the second line as well, and one of the newer questions in the area of CML with our patients who have stringent molecular remissions is is there a subgroup that has been cured or can you stop? So there is a study currently going on for patients who stop their TKI and see if they're truly cured, so it looks very different.

Then I'm just going to switch over from the MPNs more into therapies about AML. Like Sandy alluded to at the beginning, you know for the past 20 years, it has been very quiet in drug development for AML. Anyone who has had a leukemia patient in their career will know that, like 7+3 is 7+3, correct? So we're going to talk about not your grandmother's 7+3 today and flavor up and listen to all the different developments that have happened. It's always interesting when you create slides for a presentation because things change even when

your slides are submitted, so it's been very exciting. Let's talk about some of these drugs and the indications for them and how they help target. Dr. Artz was talking about FLT3 and how it often portends a poorer prognosis for the majority of our patients, and it is something that is present on normal myeloid and lymphoid progenitor cells, but it's also expressed in leukemia cells with about 80 to 90% and about 8 to 10% of these folks have a TKD mutation, and it leads to an overexpression of this and an increase in cell proliferation. So historically these are the people who just didn't do very well; they have very proliferative, they would come in with very high white counts, short durations of remission if you could get them into remission.

At the beginning of this year, I would say that 2017 has kind of been the year for AML drug development. Myeloma had their day in 2015 when they had a plethora of drugs, so I'm glad that things in AML have finally started to unfold. And in April this year, the FDA approved the first drug since the year 2000 for acute myeloid leukemia and it was the drug midostaurin, and this was the study that was done in a very large cooperative group setting and this drug is a FLT3 inhibitor. It is an oral drug as well, and the schema was that folks were randomized to either 7+3 and midostaurin, which is an oral agent, or 7+3, and the study did meet its primary outcome objective, which was improvement in overall survival. The five-year survival rate for the folks who got midostaurin is 51% versus 43 in the standard of care arms. What is midostaurin? It's approved for the treatment of adult patients with newly diagnosed FLT3-mutated AML, which can be difficult to get when you're sending that panel off of your site to get

it back. The dose is 100 mg a day with dose 50 mg twice a day and it's given on days 8 through 21 with induction with 7+3 and then again with your consolidation therapies on days 8 to 21. In the clinical trial, the drug was given as maintenance for an entire year, but the FDA did not approve that indication, so this is the on-label way that you give this. It's also not indicated as a single agent for the treatment of AML. So it's used in concert with 7+3. And this is the overall survival curve, so you can tell in the blue that the folks who got the midostaurin had a better survival curve than the folks who just were receiving standard of care. And there are a number of other FLT3 inhibitors in clinical trials because the disease itself presents an unmet need; yes, we have a drug that has shown improvement, but we are not there yet, so we still need to improve. A number of these drugs are in clinical trials, you may or may not be using them, but I would imagine that a few more are very close to approval.

The next drug I'll talk about is something called liposomal cytarabine and daunorubicin or CPX-351. This is not your grandmother's 7+3, right? This is a drug that's given as a drug and it's mixed together and it's a bimolar liposome, and it's a very effective drug, and it's selectively uptaken in the bone marrow and in the cells and the malignant cells for folks who have AML. It is intravenous, and then you can tell that one unit of this dose if you—I'm fortunate enough to work at a facility where we have pharmacists that do our mixing, but if you have to mix at your institution, you can see that one unit of this drug is equal to 1 mg of cytarabine plus 44 mg of daunorubicin. And so the approval for this is very interesting because this drug got approved for adults who have newly diagnosed

therapy-related AML or AML with MDS changes, so it's the first time we're seeing a specific category of AML patients being targeted for the approval of a certain drug. It's given on a 1, 3 and 5 schedule for induction, and if people fail to achieve remission at the midpoint, then you can do a second induction on days 1 and 3. The study was a phase III randomized, and they were older patients. Remember that AML unfortunately is a disease of older patients in the sixth and seventh decade, and they had decent performance status and they had improved survival as well. So the median survival was 9½ months versus only 5.9 months in the standard of care, which is just 7+3, and it also demonstrated superior efficacy over 7+3 as well.

Gemtuzumab ozogamicin was approved in 2017 just in September, and it actually has a couple of approvals at different doses and so the new approval is for adults either with newly diagnosed or relapsed, and it's given at 3 mg per metered square on days 1, 4, and 7, and then they can also go forward and receive consolidation as well. And it also has another approval for people who have relapsed AML as well, and it's also approved in the pediatric setting, which is something we usually don't see. This drug is something old and new again because it was on the scene back in the early 2000s and pulled by the FDA in 2010 as the studies didn't meet their primary endpoint and it was shown to have a lot of toxicity, so it continues to demonstrate myeloid depression, and then hepatic toxicities are always something to pay attention to with this agent as well. We talked a bit about IDH-mutated AMLs and how the IDH is present in about 10 to 12% of these patients. And we also now have a new drug called enasidenib,

which is an IDH2 inhibitor, and it plays a very important role because this drug is indicated for patients who have relapsed or refractory AML. This is the study that brought to approval enasidenib, and it had an overall response rate of about 38% with some complete responses, but then a number of other responses with incomplete hematological recovery in people who had stable disease. This also is an oral agent; it's a tablet. It comes in 50 mg, and it's 100 mg daily recommended dose. They can take it with or without foo. And the very interesting thing about this agent is that it causes differentiation of the leukemic blast cells, and what can happen when people go on this drug is something called differentiation syndrome.

If you've ever worked with a patient who has APL, which we are not talking about at all today, those patients can have very high white counts and go into tumor lysis syndrome. So you have to be astute and be aware that this drug can cause it. And since it's an oral drug, your patients may or may not be hospitalized. If they are coming to see you frequently in the clinic, you are going to need to carefully monitor that as well. It also caused some liver toxicities, elevated bilirubin, and people stay on this agent until disease progression, so another oral agent as well. There are a lot of other drugs that are being studied in AML, many in clinical trials both single agents and combinations. Many of them are, again, looking at targeting unique markers, but they're not approved and there's just not enough time today to talk about them, so we are not going to. When we talk about our patients with AML, what we're trying to do also is beginning to shift our goals of therapy for patients from simply treatment to cure.

I'm going to let Dr. Artz start talking about stem cell transplant as an approved therapy.

DR. ARTZ Thank you, Dr. Ridgeway. So the last part builds on two ideas here; the first is that of course with a lot of the myeloid malignancies, we still are not at the stage where we feel that we're likely to achieve long-term control, and alginate transplant remains the best option for many patients. And the second is, especially at a meeting like this, which is so important, to talk a little bit about collaborative practice and the role, essential role, APPs can have in a collaborative group managing intensively treated myeloid malignancy patients. We know that, generally speaking, for intermediate or high risk—and I showed you the ELN classification—for younger patients, we would recommend alginate transplant if the patient is considered fit enough and your center finds an appropriate donor for them. And for older patients, we would also consider it more and more depending on your center criteria. The other indications would be in addition if you had induction failure, and if someone had a relapse and hadn't pursued a transplant, all of those would be very high-risk disease settings. But for the older patient it's really a struggle. Many people in the room have faced this trying to help their patients navigate the illness because the patient wants to do everything to get better, but doesn't want to do everything to get sick.

A lot of times we're forced with, okay, we can give you intensive therapy, perhaps make you sick, perhaps live longer, even go to a transplant or take a gentler road. And these are very difficult decisions that we face, and the more we have available therapies, the more we face these difficult decisions. What's

happening in the field though right now, transplant has exploded in the older adults, and anyone who is at a transplant center knows this. Actually all of the growth in alginate transplant has occurred in those 60 and older. If you think about people under 50, there is a decline each year in the number of allografts being done for patients under 50, but in the older patients, it grows. And actually the most rapid growth is in the 70+ group, and it's the very top bar, it's that orange top line, but if you go back about 10 years ago to now, it's still a small fraction, it's about 4%, but it's risen 10-fold, so that's where a lot of the growth is occurring and that's where in the future we expect to be, and this is for general malignancies.

Now in the older patients—and let's just use 70 because that I think for most people would say allograft for 70 and older that is definitely an older group. These are some recently published data from US centers that report to the transplant registry the most common disease is AML, that doesn't surprise anyone; you can see it in the blue. In the green, you see myelodysplastic and myeloproliferative syndromes merged because that's how it's classified in the registry. That green arrow, something very important happened on that time period and that was Medicare allowed older adults to get transplant under some coverage decision, so as long as they consented to have their data submitted to the registry. There's a study that's looking at the benefits. Then they said we will cover—it's going to be a covered benefit. So just by allowing coverage to occur, it shot up. The same thing is going to happen in myelo—or has happened in myelofibrosis. There's now a coverage decision that's going to allow Medicare

recipients to receive it, so that's going to go up as well. The point being is there's a large reservoir of older adults that people may want to offer transplant to. There is a lot of reluctance and a lot of different reasons, but insurance has been a major limitation, and that barrier has increasingly been removed at least as of today. How do older adults do is always a question.

These are data for patients who have AML by age in first remission, and what you can see if you look at the absolute numbers as I said before, the 60+ groups still comprises quite a large number of transplant for AML. You can see almost 4,000 in that time period, very few auto grafts done, which is expected. The survival, one-year survival, doesn't tell you why people didn't survive, is lower in people who are older, that doesn't surprise people. It's about a 15% penalty compared to younger adults, that people do worse, and maybe 17% or so for people for three-year survival. So they do worse than younger patients, but that's really not the right comparison, and I think a lot of comparisons that people have done comparing younger to older, it's not very useful. If you look at data for AML, the blue, here's some data of AML patients and the blue under 60 and then the yellow 60 and older, and just by using that age cutoff in cytogenetic categories of favorable, intermediate, and poor without molecular data, there are very big differences, and basically older adults with the same karyotype or cytogenetics do worse even given standard induction and consolidation.

The disease tends to be worse. When we do molecular panels, you start to see some of that, but the bottom line is that our standard approaches are not doing a great job of achieving long-term success in the older adults. So even

though older adults might do worse with transplant, it doesn't mean that it shouldn't be offered, it still perhaps may be of benefit compared to standard chemotherapy, but there's considerable toxicity that occurs in older adults as we know and anyone who's trying to decide if they should offer that to a patient or recommend it if they ask you, you are concerned about their ability to handle it and what's going to happen to them, as is the patient, as is the family. And the way we look at it is we think about chronologic age versus resiliency, and we can use that information to help not only inform candidacy, but what we really want to discuss is how you can use that information to optimize the outcome, not just to say yes or no, but to say how do we do, yes, better. If you think about unfit, we all have an eyeball test that says, okay, this person maybe unfit, they seem to have a lot of issues, and this person is fit or resilient, she ran seven marathons in seven days across seven continents. This is actually true at age 70.

Typically transplant though had been looked at in younger adults, we just—and a lot of the criteria were old school criteria based on exclusions, that is, if you weren't excluded, you're included, and how do you decide exclusions? Well, you have severe end organ dysfunction, just like a study, you just copy it over. These are some transplant consortium studies that reflect standard practice. At a certain age someone might be ineligible, a certain LVEF too low, abnormal liver tests, kidney tests, abnormal pulmonary tests, cardiac, cancer, prior cancer, low performance status or KPS, and those are probably important, you may not want to offer a transplant to someone with severe end organ dysfunction, but for people who aren't ineligible who are older, does that make

them eligible, does it make it a good idea? There are a lot of vulnerabilities that, of course, exclusion criteria do not capture. And I think, Jean, I'll turn it over to you to talk a little bit about the transplant optimization program and how we go about trying to assess resilience in an interdisciplinary team approach.

DR. RIDGEWAY Thanks. One of the things that Dr. Artz and I work together on very closely is our older adult clinic where we seen patients who are age 50 and older considering an allogeneic transplant. Our absolute cutoff for autos is 70, although we'll see 60 year olds who are heading to autologous transplant. The core of it is looking at that nontraditional assessment to get a better understanding of resiliency versus frailty using a tool that's well known in the geriatric literature called a geriatric assessment. And so we look at these domains, comorbidity, functional assessment, cognitive, emotional social support, nutrition, and polypharmacy, and we have the patient and their primary caregiver and family come in for a half a day assessment, but when we look at our comorbidity domain, we look at some relatively traditional measures. We look at their comorbid conditions; do they have diabetes? We look at their pulmonary function tests, their ejection fraction, and then we do something called an HCTI, which is a toxicity criteria that was developed by Dr. Sorror and colleagues up in Washington that has a number of grading criteria for specific disease, and we look to see if the patient has a vulnerability. So in this instance, if the patient has diabetes and depression and osteoarthritis and a creatinine clearance of only 50, we would say that with their comorbidities, they have quite a few vulnerabilities that need attention in order to optimize their outcome. So as the patient moves

forward to transplant, we want to ensure that for this patient that endocrinology is present on admission and that they're limiting nonsteroidals for their OA treatment as well. We do some functional capacities, we do something called a six-minute walk test. There are age-matched normals to see where your patient is, as well as we ask them about their ability to do IADLs. In the geriatric literature, it has been shown that patients who have one or more impairments in their IADLs have worse outcomes, so I've heard someone say that IADLs are the things that your children need to do when they go to college, so you think about they have to be able to—who pays their bills? Who drives their car? Who does their cooking? Who does their bathing? Who is handling their medications? As you look at that with your patient, as you have a discussion looking forward to an aggressive treatment, having any one of those areas needing assistance tells you that the outcome is not going to be as good.

When we look at also their time to get up and go, we look at grip strength, and many of our patients then are recommended to have prehab either in the home or out of the home—we think having PT out of the home is better. We have a physical therapist as part of our team and we look at cognition, we do a Blessed Memory Orientation Test, but if it looks like they are going to have vulnerabilities we do recommend a full panel cognitive testing. We ask about anxiety, coping, do they feel depressed? Some people have a very intact social system, some people have one that is very sparse, and even getting these folks to see psychiatry if they've talked about even having anxiety and poor coping

mechanisms before they move to transplant, getting them engaged and getting our psychiatrists and psychologists on board as well.

Social support is key to help people get through this, right? And so initially for this patient, at least you know it was poor, but then later they mustered their resources, and having family meetings is very important before they go. One of the things we've found that patients do better on the inpatient side is if they have a caregiver stay with them during the time of neutropenia. I say you have to engage a lifestyle coach and the person can be there encouraging them to eat, sit up, walk, etc. And then we also look at nutrition for all of our patients. Nutrition is something at least in my perspective as a provider I have not a lot of training in. And it's interesting in the literature, if you look at unintentional weight loss, 10% unintentional weight loss over the past six months for your patient, also will prognosticate a worse outcome for them. And unless you go back and look at the chart and are talking with your colleagues about it, it very easily gets missed and patients become sarcopenic and deconditioned very quickly, so that needs to be optimized. A lot of our patients come in and may take more herbals and supplements than they do traditional medications, which can have a very large impact. Some of it for us then is re-educating everyone. Then we look a polypharmacy and how many medications they currently are on and which ones to stop, and you'd be surprised how many people will comment that they remain on medications that somebody else thought they had stopped, so vetting that medication list when you meet with your patient, although it can get very routine, is critical to success.

DR. ARNTZ This is a team sport. So one of the things—speaking about resilience and the geriatric assessment—one of the concepts if you think about it is resilience for the short-term treatment of a myeloid malignancy with intensive treatment, like an allograft, we think of it as accelerated aging. And one way to think about it is if you look at factors that predict long-term survival in someone who's not getting intensive treatment living in the community, these are the factors. If you do one of the calculators to say what's someone's estimated prognosis, a community-dwelling person 50 and older and these are points, and the more points you get the average, the worse the 10-year prognosis. This is irrespective of cancer and you can see. So older age is adverse, of course, the more points, the older the age. Eighty-five year olds are less likely to make it 10 years than a 70 year old, but just as important as some of these comorbid conditions is diabetes and low body weight and not high, and you would think non-skin cancer or cancer would seem ominous, but difficulty bathing as Jean said, one of your activities of daily living, difficulty with finances, an IADL, difficulty walking several blocks, and difficulty pushing large objects, and when someone says, "I'm a little bit weak," we have to ascertain this, so this is the type of information that we hypothesize that if we applied it in some intensive setting that it would be important for short-term effects. These are ways of measuring resilience, function, functional capacity, and disability in addition to comorbidity and age.

At our center, we have been doing this for 12 years now, doing some type of assessment, and in our initial work, what was really surprising and this is

before we had a clinic and we had to prove to our physicians that getting more information was useful, so we just did a geriatric assessment at the time and collected these domains. We call this our toolbox or geriatric assessment toolbox; this was the one at the time and not the one we are using today, so we captured a frailty index, that's a validated tool, impaired physical function by a short form 36, the SF36, emotional or mental health by the SF36, again, all just routine quality of life questionnaires. IADLs, seven questions about your instrumental activities of daily living, comorbidity index alluded to, tabulation of your comorbid burden, and a CIRS-G is another comorbidity tool and CRP as a biomarker, and all these patients were 50 and older with blood cancers who went to transplant.

At baseline, there were somewhere between 15 to 50% of those patients had vulnerabilities or limitations going into transplant, and other centers, MD Anderson, did this later, Holly Holmes, and found the exact same thing, that a very high frequency who are older going into transplant selected by their physicians, vulnerabilities were really frequent. And if you look, this is the present geriatric assessment that we use today from Arti Hurria's City of Hope, and the ones underlined are some modifications that we use at our center, but all of our patients undergo this essentially before they see us, although there are some bedside tests on cognition, but they do the questionnaires before they see us, so we know when someone comes in and the whole team knows when they come in, okay, they've had weight loss, their emotional health is good or bad, we've already done a good screening test, but it's just the beginning. Once you have

that information, now the providers can come in and really use that information to better ascertain limitations and strengths. This is what we recommend to every person; we have a tailored approach and a non-tailored approach.

Every person who we see who we have any vulnerabilities, we just try to give them the maximal support, so you can say, “Well, your function is poor to go to rehabilitation,” but you know these things are often multifactorial, as you know. Someone who’s not walking very fast, there are other reasons, they may have comorbid conditions, maybe they didn’t have good social support in the hospital, maybe they had infection, so you can’t really look at a single domain and think exercise or nutrition is going to fix everything. We work with a philosophy that if we are going to treat you intensively and there are some vulnerabilities, we better create an ecosystem that gives you some reserve, and that way, if one part of it isn’t treated, let’s say your function didn’t get up there, but we fixed your nutrition, your social support, your infection, and other issues, maybe you will still be able to get through because now we’ve created a system of reserve, of resiliency or helped you create a resilient system, and it is about not just the patient, but we caught the ecosystem, the family members, the environment you’ve created, the attitude, the team that participates—it’s an ecosystem. And here are just some of the individual things we do. We talked about 24/7 caregiving, prehabilitation.

I think a lot of people here recommend it. Delirium precautions; it’s educating the family because the providers often don’t know how to recognize delirium until it’s pretty severe. It’s better if the family knows how to recognize it and obviate it. Then we would see them again at day 30 after a transplant

because everyone has taken a step back after transplant, and we look at where they are and try to establish a difference from the trajectory that they are on at that point and try to make sure it's an upward trajectory. Is there anything else you wanted to talk about?

DR. RIDGEWAY When we look at the high comorbidity and functional limitation that influence overall survival, for patients who are age 50 to 59, it's obvious that if they are both abnormal, both IADLs and their HCTI score, their comorbidity score, you can tell that they're the bottom of the line. But if both are normal, their overall survival and success is better, and if you look at the group of patients who are age 60 and above using that same criteria, you see that they begin to separate out even further, so you know having both as an asset, maximizing their IADLs and having an HCTI score, it is what it is, but it's a good baseline to know that even with one of those impaired, their overall survival, the data tells us that it's inferior and the green line is our resilient folks. We'll talk a little bit—this clinic that we have is called the Top Clinic, and it's dedicated in our disciplinary team and it was the result of the work of Dr. Artz, and I'm fortunate enough to be a part of it. It's a true interdisciplinary collaborative group, and what we try to do is offer individual supportive care plans for each patient that we see. We have two different categories; we have standard optimization, so the patient is basically a green light with the attending physician, they've met all the basic criteria, they are going to go, but then they ask us to see the patient and see if there can really be any areas to optimize.

Then we have an eligibility assessment, so if you have an old—our patient's going to an allo transplant, they are in their late 60s, perhaps they're obese, they have diabetes, they had a bad fungal infection during their course with AML, try to tease out where are they, and they may or may not go forward. Sometimes our patients can be delayed, and we recommend delaying, it becomes a very tenuous decision. I leave all the difficult decisions to Dr. Artz. But with AML as you can see, it's a difficult disease to treat and you cannot delay too long because the disease by itself may continue to progress. You are not going to stay in remission forever. So how do we do that? We recommend then things for our patients that are definitely tailored to their needs, we don't have a one size fits all. We do see definite trends in vulnerabilities and we make recommendations based on that and we come up with three different categories that these folks land in that there aren't any issues, we may make some subtle recommendations, but the patient is good to go forward to transplant. Then there's the maybe group, that's the gray group to defer, that there may be some hindrances. Perhaps their six-minute walk test—maybe they were only able to walk 100 meters or 150 meters, they don't have a caregiver, they have no transportation, so you know they need to see the cardiologist to have their ejection fraction optimized. If there are things that can be addressed in a reasonable amount of time and then continue to safely move forward, then that's what's recommended. Or sometimes we do say no to patients whose comorbidity score and their current health status definitely preclude them from going forward with a stem cell transplant. Here's one of our patients as an example of what we

usually see. Our clinic happens on Friday, and we tell our patients “Be prepared, be comfy, bring a lunch, it’s all day.” So they arrive at about 8:00 o’clock in the morning and they are with us until about noon, and then we meet as an interdisciplinary group and we discuss the cases. We can see three patients; that’s a bit of a stretch because there are seven or eight of us that need to see the patient in that time period.

Here’s a 70-year-old woman who comes in with AML. She has a normal karyotype, no TP53 deletion. She did evolve from MDS, and so she did have treatment with azacitidine. She did fortunately go into a complete remission. We look at her and she’s going to have an allogeneic transplant; she has a 10 out of 10 match unrelated donor, CMV seropositivity; her KPS is 80%, and her score is 2, and each of these has a score. You can look up Sorror and look at it, but you know even with a score of 2, that doesn’t sound very significant if you’re not familiar with it, but we know even with an HCTI score of 2, it does differ—it gives us an inclination that it’s an intermediate type of risk. She is forgetful at times, she’s got knee pain and hip pain, she wears partial dentures, she’s widowed, but she has children in the area. So when we think about what vulnerabilities we are identifying even from this brief history, you can’t really see the red line so well, but a KPS of 80% is less than optimal. So she is up and about quite a bit, but she is not as functional as we would like her to be.

She does have a history of depression of some sort, either she mentioned it in the history or perhaps she is on some type of agent, and to dive into that, what does it mean, what does it look like, you know are we going to refer her

over to our colleagues in psych. Forgetful at times means a lot of different things, and so doing a little bit more cognitive testing we do something called The Blessed; it's a simple ER test, but you can do than a MoCA test on them or refer for cognitive testing. She would definitely be someone that would be going for a half a day of cognitive testing. Patients hate it; it's just being grilled, it literally is a half a day of testing, but then what it does do is it identifies domains where people have difficulties. So she's forgetful, she also is widowed. It gives you an insight to where she's living, is she living—she has children in the area—but is she living by herself? Who's going to take care of this 71-year-old after a transplant? So lots of that. That raises a lot of red flags. We love our social worker, he does a lot of hard work with that, and so we all meet together then after we've seen the patient and we give our input.

We go around the table and it's always insightful to hear sometimes a bit of a different history. They give me a different history or to the nutrition or physical and then to see what their actual physical function. We have a physical therapist that's part of our team that does muscle testing, strength testing, and as we go around the room then, we come up with pretty much a consensus recommendation, and we have formal written recommendations that are provided then to the primary transplant physician team. I get the lovely duty of writing the note, and then I also circle back with the patient. I say to them when I meet them, "I'm going to call you on Monday and we're going to talk about what's recommended." Most patients are pretty nervous when they come and see us, they see us as the gatekeeper, right? No one wants to stop treatment, and

sometimes we're perceived as someone who may be the obstructionist and not allow them to get their treatment. So as the morning rolls on, many times people warm up to us, but sometimes that gets a little worse as the day goes on—it all depends.

We circle back with the patient and the family with our recommendations and then the follow-up. So this is what it looks like. Once a patient is identified by the primary service, say the multiple myeloma team tells us that Mr. Smith is coming forward; he's finished his induction therapy, we're going to collect him. He's identified and then an e-mail is sent out with surveys and the different questionnaires that they fill out so we can have an idea of their cognitive function and their IADLs, the interdisciplinary meeting, that's at the end.

All those boxes were team members, but represented on our team. Dr. Artz is our transplant physician, he may or may not be the transplant physician for the patient. We have a geriatric oncologist, a social worker, we have an infectious disease physician, physical therapy, we have a dietician that meets with us, I mean, with the patient. Who am I forgetting?

DR. ARTZ We have our research --

DR. RIDGEWAY We have our research --

DR. ARTZ Research coordinator. I think you've got it.

DR. RIDGEWAY I think that's pretty much everyone. That's our team. We believe in an integrative model in transplant where we know that the resilient phenotypes really allows risk stratifications amongst adults, and we like to get our patients as optimized as possible, and the multidisciplinary clinic is a great way to

practice a true collaborative practice you know as we assess patient's vulnerabilities and hopefully improve their outcomes and expand the transplant eligibility for them. These are our conclusions.

DR. ARTZ All right, so. It's getting late, but myeloid—classification of myeloid malignancies; you've heard it requires genetic information and history, you guys are essential to that. The genetic landscape that you obtain will inform prognosis and the therapies. We've heard from Jean about some new therapies available including the oral inhibitors for FLT3 and IDH2-mutated AML. Our advance practice providers play a central role in managing this continuum of myeloid malignancies as well as a central role in a multidisciplinary team approach to help manage complex patients or treatments and is a model that perhaps others could utilize as well. We really appreciate the time and patience.

[END]