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TRANSCRIPT - GR 11 22 24 ***"Myelodysplastic Syndrome: Improving Outcomes Through Progress and Resilience"*** guest speaker Daniel Reed MD, University of Virginia

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Internal Medicine Grand Rounds

- All right, everyone, thank you, and welcome to medical grand rounds. We're excited to have Dr. Danny Reed with us here today to talk about myelodysplastic syndrome. I'll take us through our Cme. Slide. So for faculty, if you haven't been at grand rounds for a while some new ways to log your attendance for Cme. Credit today's activity code. And then our chief resident, Dr. Shaina Hassan, will introduce Dr. Reed.
- Right?
- So in here, maybe twice. Okay.
- now, we're up for Dr. Reid. Thank you.
- All right. Good afternoon, everyone. It's my pleasure to introduce Dr. Reed. Dr. Reid obtained his medical education at Drexel University, went on to complete his internal medicine and hematology. Oncology, fellowship. Here at Uva he was assistant professor at Wake Forest School of Medicine. Before returning here in 2023. As assistant professor in our Hematology Division.
- Dr. Reid's research is deeply focused on advancing treatments for hematologic malignancies, particularly myelodysplastic syndrome and acute myeloid leukemia. His work has led to several impactful publications and ongoing clinical trials, and is principal investigator on several industry and cooperative group studies. Notably he has contributed to exploring the therapeutic potential of decidabine venetoclax, and other targeted agents in Aml.
- Dr. Reid is also an accomplished educator and mentor, fostering the growth of future medical leaders through direct mentoring and teaching, and I can say from my own experience, our residents are very much a fan when you attend on the Hematology service. His dedication to evidence-based clinical care and innovative research exemplifies his commitment to improving patient outcomes and hematology and oncology. And we're very pleased to have him speak to us today on progress and outcomes and myelodysplastic syndrome. So please join me in welcoming Dr. Reed.
- No, okay, alright.
- does that work. Can you hear me. Okay, perfect. I talk loud, anyways. So I'm going to go over the kind of the landscape of myelodysplastic syndrome today, I've got nothing to disclose.
- So 1st we're going to talk about you know what is myelodysplastic syndrome who gets it and then kind of how it's diagnosed, how it's staged, and then what ultimately is the treatment of Mds.
- So let's start with what is nds.
- And when I 1st meet my patients in the clinic, and I'm talking to them about a very complicated, you know, bone marrow situation. I really like to kind of hammer down on a concrete example that they will understand. I really enjoy the example of the

factory. And so, you know, we have raw material, the iron, the B, 12, the copper, the folate. We have our factory.

- and out comes the product, red cells, white cells and platelets. This schema. I use a lot when I talk to my patients in the inpatient side and outpatient side.
- So we'll start with what is myelodysplastic syndrome? The M in myeloid, dysplastic syndrome is myeloid. So this is the cells that give lineage to your red cells, your white cells and your platelets.
- And if we zoom in on this factory, what we're really talking about is the myeloid portion, and we're going to leave our lymphoid lineage for another talk in another day. Specifically, we're going to focus on the myeloid lineages of the red cells, white cells and platelets.
- The D stands for dysplasia. I really like to think of this as clonal destruction, because it's really your bone. Marrow has acquired, you know, a lot of mutations and chromosome changes from toxins in the environment, and you have a broken factory. And this is kind of what myelodysplastic syndrome is and what causes it. And then, as you can see on the left, we have some examples of
- red blood cell dysplasia, and then we have some ringsideroblasts. So we'll see that under the microscope. Whenever we do a bone marrow biopsy.
- we have evidence of dysplastic megakaryocytes, so platelets that don't look normal. That are bilobed or hypolobulated, and this is kind of the definitive definition of dysplasia in the Mds. Syndrome.
- So syndrome
- really stands for bone marrow failure. These patients are extremely symptomatic. They have fatigue, malaise bee symptoms, night sweats, weight, loss, bleeding, bruising, and infections. And you know, a lot of my patients will describe to me, Doc, I just really feel like. I can't get up and do anything. I feel like. My legs are encased in cement.
- So this is kind of a definition that I took from both the who and the Icc. We'll talk more about that in a little bit, but it's a clonal disorder. It's derived from stem cells. It's characterized by low blood counts, and it's really characterized by dysplasia so abnormal looking cells under the microscope with a propensity to bone marrow failure and acute leukemia. But what this really means
- is that myelodysplastic syndrome is a cancer. It's a myeloid neoplasm.
- and you'll see in a little bit why, it does us no good to talk about pre leukemia states with patients. This is really indeed a cancer of its own, and needs to be kind of treated seriously when when discussion with the patient.
- Now we'll talk about who gets Mds. And we'll start with a case that kind of outlines who we expect to get Mds. So we have a 74 year old female she presents to the emergency room. She has fatigue, she's had these symptoms that have worsening over the past 6 months.
- She has no B symptoms, but she does have a past medical history of breast cancer. This was treated surgically without chemotherapy and an adjuvant aromatase inhibitor, and she's coming in. We see her white count is normal. Her platelet count is a little low, but it's normal. And then her hemoglobin is 6.4 and a Mcv. Of 110.
- So this really kind of highlights, 1st and foremost, the significant risk factor for myelodysplastic syndrome which is age. And we'll talk about. Why, that is in a little bit. But the average age of Mds is 73. You can see that it gets more and more as we get older. So the incidence goes up and men are 2 times likely to get Mds. Than women we'll talk about. Why, that is this is probably way underdiagnosed.

- you know, elderly patients are at their Pcp. They have so many comorbidities, and the macrocytic anemia that's just been hanging out for years. Isn't really something that is top of mind whenever we're evaluating these patients.
- So we've known for a long time that benzene chemicals, petrochemicals, radiation really can cause patients to get Mds. So if they have environmental exposures like that, those are patients that will get it. And then we have treatment related, which is a lot of my patients who have Mds, they've had a prior cancer lymphoma, breast cancer, and they've been cured of that cancer.
- But they've been exposed to topoisomerase inhibitors and alkylating agents. And so they have cytogenetic changes that are associated with those agents. These are quick board level questions, especially for hematology, fellows. This is good to know. So your Topo, 2 s. Are 2 year latency and associated with Mll. Rearrangement.
- and then your alkylating agents are really the myelodysplastic syndrome over time 5 to 7 years. Monosomy 5 and 7. But we can't forget chronic immunosuppression with our rheumatologic colleagues seeing lupus and other autoimmune conditions when they're on chronic immunosuppression they're also at risk.
- This is kind of a shocking one.
- So one of the big reasons for Mds, and one of the reasons why the average age is is what it is is because you get one protein coding mutation every 10 years
- per hematopoietic stem cell. So if you say you have 50 to 200,000 stem cells. You are accumulating close to a million protein coding mutations. By the time you're at the age of 70 I don't mean to scare everyone in the room. It's amazing that we're not all walking around, or the older patients are not all walking around with myelodysplastic syndrome.
- These cells gain clonal advantage. So they actually become dominant over the normal cells and start to expand.
- And so we're going to talk a little bit more about that these mistakes that occur in particular epigenetic machinery. So you remember from your cellular and genetic biology that you have epigenetic control, which is acetylation and methylation patterns and histones and promoters. And so these are the enzymes that are involved in that.
- and then splicing machinery is really important in myelodysplastic syndrome. So you have introns and exons. If you remember, you kind of can weld the exons together in different forms, which leads to different protein isoforms. These mutations are extremely important in myelodysplastic syndrome.
- So we're starting to learn we're starting to get more progress. And who gets Mds. We have this new entity called clonocytopenias, which really means that the patient has a mutation they don't have the dysplasia to define. They have Mds. But maybe they have a low blood count Anemia or Thrombocytopenia. They're going to meet criteria for ccus
- if they just have a mutation that's found, and they don't have any blood count abnormalities. They're going to have something called Chip. These 2 Icus and Idas are less kind of significant in this talk. So we'll focus on chip and ccus.
- And this is kind of why males are increased risk for Mds. So you can see as you're, you know, young, and you've got, you know, normal hematopoiesis. And then, as you get older, you get exposed to chemotherapy. Maybe you've been unfortunate enough to get a Y chromosome, and you have a germline disposition or smoking,

and you're really going to see that this predisposes patients to clonal hematopoiesis which predisposes them to myelodysplastic syndrome.

- Hot off the press. This was just published in blood. This is a calculator to kind of see, you know, if I'm evaluating a patient with clonocytopenia, what's their risk of getting a myeloid neoplasm?
- And really, these splicing mutations that I talked about a low platelet count, and the significant number of mutations is really significant for these patients. With myelodysplastic syndrome on the right you can see that they separate pretty well. But the patients that are at high risk are really high risk for developing Mds and Aml.
- And then we're really learning. We're gaining more progress in inherited causes of Mds. So we all know Fanconi's Anemia, Schwalkland-diamonds, Syndrome, and the Telomere pathologies that Span the course of internal medicine so cardiology, dermatology, pulmonology, and hematology.
- and they're associated with Mds. But then we've also started to learn about new ones. So Ddx. 41. And the thing about Ddx 41 is, you don't know. You have it until you're fifties, sixties, seventies, and you present with Mds. And now we're finding that Ddx. 41 is really important. This has implications for patients who are moving on to stem cell transplant.
- So now we've talked about what Mds. Is who gets it? We're going to talk about. How's it diagnosed? And we're going to go back to our case. Remember, this was a 74 year old female. She had new macrocytic anemia. And we're going to start with the anemia workup. Right? We're going to look at this. And we're going to decide. Is this a material problem? So we get. You know, the vitamins and minerals, especially copper, zinc, iron, and B 12.
- We can see that she has completely normal copper, iron, methylmalonic acid. B, 12. So we don't think that this is a material issue. She does have a hypoliferative anemia. So her retic count is 1.5%. So something's going on. But we really need to do some more investigation we can talk about. Is this a destruction problem? Is this something where she's losing red cells? Is she bleeding because this is really common for a 74 year old female.
- So we get Hemolysis labs. Maybe we talked to her about gi bleeding symptoms, and she tells you, no, she doesn't have these. She's negative for Hemolysis. So really, what are we looking at? We're looking at a problem in the factory. Something's broken.
- And you know this can be because there's invaders. So there could be hepatitis. There could be. Ebv. Hsv. Cmv. Those viral illnesses can cause suppression of the bone marrow factory. But it could also be unfortunately, a bone marrow cancer. So quick question, what do we do next? Do we give for just observation. Do we say that this is just normal trial of B, 12 bone, marrow, biopsy or folate?
- Yeah, thank you. So bone marrow, so as you can see on the right, you know, this is kind of a picture of how we do a bone marrow biopsy. We go through the outside cortex of the bone into the medullary portion. We pull out liquid blood, and we also get a piece of the bone marrow with a jammed, sheeting needle.
- So you do her bone marrow biopsy. And this is an oversimplified report, but she has a hypercellular marrow, so more cells than she's supposed to have. She has erythroid dysplasia. So there's abnormal looking red cells, and she has increase in ringsideroblasts. The aspirate confirms this dysplasia. No increase in blasts.

- Blow confirms. You don't have increase in blasts. Her molecular markers are significant for an Sf. 3 b. 1. Mutation and her chromosomes are significant for deletion 20. This all means something to us as myelodysplastic syndrome experts trying to help this patient out.
- So how is nds diagnosed? How did we tell this lady? You have myelodysplastic syndrome? We really look at a threshold for dysplasia at 10%. This means that you have to have a top notch team of pathologists which we're lucky to have the best here.
- And you really need to be defining. Is this enough dysplasia to call myelodysplastic syndrome? There's clonal cytogenetic changes about 50% of the time of note monosomy. 5, 7, and complex cytogenetics do not require dysplasia. So you can actually give a patient a diagnosis of Mds without it.
- And there's molecular changes around 90% of the time, because of everything. I've just talked about all of the mutations that are occurring over the years of exposure.
- So we're lucky enough in malignant hematology to have 2 warring factions in defining what is the definition of Mds. And Aml. And also lymphoid disorders. We have the who and we have the Icc.
- So these have been recently updated. I like to think of the who as the kind of the nerdy pathologists that are seeing what they're looking at under the microscope, and then the Icc, as really the nerdy clinicians that are kind of, you know, treating the patients and trying to decide what is the next best step for my patient with diagnosis. They're pretty similar. But I want to call attention to
- this entity, which is the Icc classification. Mds slash Aml.
- and you can see that these are patients that have excess blasts. So excess leukemia cells. So you're only supposed to have 5% of blasts in your bone marrow and less than 5%.
- And if you have 10 to 20%, the who calls this Mds with increased blasts and the Icc says, No, wait. This might be more consistent with acute, mild leukemia, and this is why so this is work that was published in blood in 2022. This has led to the Icc classification changes. This was a retrospective study. Large Fred Hutch, looking at a lot of patients that had the diagnosis
- of Aml, 202 patients that had a diagnosis of this 10% to 20% blast. And does having this definition really affect your outcome? And the answer is, no.
- So if you look at the survival curves and you control for a host of things that would impact a patient's prognosis with Mds. And Aml. You see that they're pretty much the same. And so this has kind of led to the revolution of us as Mds doctors, taking these patients with excess blasts, and really giving them therapy that is offered for acute myeloid leukemia, being able to enroll them in clinical trials. That's
- really only operate in acute myeloid leukemia, because we know that they're going to do just as worse as patients with Aml.
- So there are pitfalls. All that is dysplastic is not. Mds, you have to do a thorough look at the medications that they're on toxins that they're getting. Ethanol is a big one. So patients who are heavy drinkers can have dysplasia, and we can have vitamin mineral deficiencies. You guys remember this ring, sideroblast picture. And let's say you do a bone marrow. You find that.
- And you say, well, that's Mds. And you fail to check the copper level and you give them God forbid! Hypomethylating agent. You've done them a really big disservice because they're probably copper deficient and have ring syneroblasts that are actually present in patients who have copper deficiency. So our job before we do

the bone marrow is to make sure that none of that's going on, so that we come up with a good diagnosis for our patient.

- The definition of cytopenias of aging is not something, so don't think of it. And patients that have hypoliferative anemia really need to be evaluated by hematology.
- How is it staged your patient sitting in front of you, and they have a loved one who's had breast cancer, lung cancer. They know that if you caught it early, you know if it hasn't gone anywhere, that it's an early stage, and that you have a better prognosis. Unfortunately, with myelodysplastic syndrome and leukemia, we stage our patients based off of molecular and cytogenetics.
- So it's been known for a long time that cytogenetics are very important in the prognosis of Mds. You can see back in 2012 we had this really nice separation of curves on the right, that kind of looks at different cytogenetic changes, and how the prognoses are impacted.
- If you take those cytogenetic changes, so if you take those and you combine them with clinical
- blast, hemoglobin platelet, count Neutrophil, count, you actually can get a new risk stratification, which is what is very popular in clinical trials. Right now, this is kind of how we risk stratify patients. But look, guys, if you're high or very high risk. Your median overall survival is 1.6 years and 1.4 years or less than a year. And so this is why it does patients notice a service to not call this a cancer? This is a big deal. The Kaplan Meyer curve show you that this is pretty dismal.
- And then, if you take the molecular studies, you combine them with the clinical studies, you can actually do even better at risk stratifying patients. And so this is not necessarily mainstream. A lot of us Mds experts are using this model to help kind of define our staging for our patients. You see, some of those common mutations that I talked about are important in prognostic. So this is a big thing to remember.
- Let's go back to our case. We see that she has a ringsideroblast. She has sf. 3 b. 1. She has deletion 20 Q.
- We put her into the calculator, and we say you have a moderate low disease. But you say, well, Dr. Reid.
- her Ipssr score says that she's intermediate, and we don't know what to do with this yet.
- Thankfully, she doesn't kind of meet criteria for a higher risk disease, but she is downstage, and the reason for this is because the Sf. 3 b. 1 mutation kind of pulls her down in her risk stratification. And so I would, you know, think of her as more moderately low risk, and she has a pretty good overall survival. And so this is how I would communicate. I usually in the room.
- Talk about the patient. I bring up their risk stratification. I sit down with them, because it's so important in myelindysplastic syndrome to have these conversations with patients.
- So now I'm going to spend the meat of my talk on you know what is the treatment of Mds.
- And the treatment is solely based on the staging. So if you have an Ipssr score that is less than or equal to 3.5. You're really going to focus on quality of life. And this is why I love being a Mds doctor, because I can not only improve.
- you know, try and help patients with their survival, but also really just focus on their quality of life. Remember this patient that feels like their legs are encased in cement. Can I make them feel better because I know that their median overall survival, if you're low or very low, risk is pretty good compared to if they're high risk.

- Let's talk about this for a second. So what does it mean to improve the quality of life of a myelodysplastic syndrome patient.
- If you have Mds, and you're transfusion dependent on a good day, you're going into the correct lab. You're getting your labs done, you know that process checking in all that takes about an hour. Then you're waiting for your type and screen that's taken, you know, some time, and then you're actually in the chair, getting your blood. If it's 1 unit, maybe a couple hours. If it's 2 or 2 units, you know, you might be spending most of your day in the Infusion Center, and some of our patients do this
- once or twice a week for for a good portion of their lives.
- Outside institutions do not get so lucky. Patients will have to come into clinic, get their type in screen, go back home, then. The next day they have to come back in, you know, get their transfusion of their blood, or God forbid! They have a low hemoglobin. Maybe it comes back at 6.4. The doc says, oh, my gosh! We got to go to the emergency room. Our patients could be sitting in there for 8 to 10 h, and these are stories that are not uncommon in our myelodysplastic, syndrome population. So this is a big deal.
- And so what's the mechanisms of anemia with patients with Mds, so here you can see you have these early precursor red blood cells. So these are really early stages, and they are increased in proliferation. They're abnormal. They're diseased. They're dysfunctional. They have a low survival. They're increased death, and they impair their rithroid maturation. So you can see these guys are going through.
- But these guys are not.
- And this is because of Tgf, beta signaling. This is going to be very important. I'm trying not to make your eyes glaze over. But tgf, Beta is really important in red blood cell maturation.
- All right. So how do we improve our patients? Lives? The Old Guard was erythropoietin stimulating agents. We know that epo comes from the kidney and and signs of distress with the bone marrow the epo comes and and facilitates the movement of maturation of these red cells, but guess what.
- It only really affects the early cells. It really doesn't affect the late cell maturation. So you can push epo all you want. But if you're arrested at the later stage of maturation. You're not going to improve the anemia. And so this is what we found out. If your epo level is greater than 500. You're probably not going to respond to Epo. Agent. If you have more than 2 units of blood per month.
- you're probably not going to respond to an epo agent, and the the response is varied around 15 to 40%.
- We have a gangbuster with deletion, 5 Qmds. And all of you internal medicine residents should remember that you're probably going to get a question of some kind on a board that talks about deletion 5 Qmds. And this is why
- you get a 55 to 65% transfusion independence from giving patients lenalidomide. This is the treatment of choice 4 or 5 deletion, 5 Q. And these patients last. This transfusion independence lasts for a long time years. And so this is why this is heavily tested on boards, because we're doing a good job here.
- and the patients also have pretty fair cytogenetic responses as well.
- And then we have made significant progress in the treatment of low risk myelodysplastic syndrome. So, keeping my patient out of the infusion center, giving them better quality of life, we have loose pattercept that came to the market in 2020, and that was just focused on ringsideroblasts, Mds. And patients who weren't responding to epo.

- And then, later on, the commands trial came out and approved loose pattercept for everyone up front. So now we can give loose pattercept to patients who likely aren't going to respond to an epo agent. And we'll talk about these drugs. And then the new kid on the block is a metal Stat.
- so loose pattern set. We talked about Tgf beta signaling
- that occurs with this late maturation right? And this is this molecule here is actually inhibiting the maturation of the red blood cells. So what do you do? You trap it? And if you trap it with loose pattercept that allows for the maturation to go through. And so this is basically what the mechanism of action of loose pattercept is
- in a phase, 3 clinical trial compared to placebo. Loose pattercept had a significant, statistically significant transfusion. Independence with patients at 38% versus 13% at greater than 8 weeks. This was its primary endpoint. It made it. This is why it was approved in 2020. This was according to the metalist trial.
- and then the commands trial was published just recently in 2024, which actually looked at upfront patients and looking at it, randomized between loose pattercept or an erythropoietin stimulating agent. So you can see a 1-to-one randomization of patients getting loose pattercept and erythropoietin stimulating agent.
- The primary outcome of this clinical trial was 12 weeks of red blood cell independence, and you had to have an increase of at least 1.5 gram per deciliter of your hemoglobin and around 60% of the patients that got loose pattercept
- responded. And had that only 31% of patients with Erythropolie stimulating agent got to that goal. And so this is really what got loose pattercept approved
- particularly. And this is kind of interesting in the subgroup analysis. A lot of the patients that got loose pattercept actually were ringsideroblast and had sf, 3 b, 1 mutation, anyways. So there's kind of like some thought that maybe loose pattercept is really good for patients with Sf, 3 b. 1. Mutation and ring sideroblast, but it's still available, and I just had a gentleman that I treated.
- Patercept was not ringsideroblast did not have Sf, 3 b. 1, and he responded to the 1st dose level and is now transfusion independent. So that's pretty cool.
- A metal Stat is the new kid on the block. And what you need to know is that Mds cells are bad and they exert clonal dominance over healthy good cells right? And so they're immortal because of this enzyme called telomerase telomerase prevents the telomeres from shortening. And so it really gives immortality to Mds cells.
- If you can inhibit telomerase you kill the Mds cell, you kill the bad guys and you reclaim the factory. The factory can then make blood again. And that's the idea. Behind a metal stat. So you have a metal stat drug. It's binding to the telomere, and it's leading to apoptosis of the cell because the telomeres are getting shorter and shorter with replication, which triggers apoptosis.
- and this allows for red blood cells to continue to mature and to make more blood.
- So a metalstat in a phase. 3 clinical trial compared to placebo, met its primary endpoint, which was transfusion independence at 8 weeks. Looking at 40% versus 15% in placebo. You guys can see, this is pretty striking transfusion independence with a metal stat placebo stinks, and that's great that it worked out that way. But a metalstat is approved for our patients with low to intermediate risk. Mds.
- And then what if your patient just has platelet count problem? There used to be old data that suggested that you can't give Tpo agonists to these patients. They're going to transform into leukemia.
- That's not necessarily the case anymore. And we really do use l-trombopag often in our patients for Thrombocytopenia. This was a clinical trial that was just published

in the Jco. In 2023 that looked at patients that got L-trombopeg versus placebo, and statistically significant difference in the platelet response. And you guys can see this lasts

- for a pretty long time, and I've had good success with my patients. So if I have a low risk, Mds patient, they don't have increase in blasts. They're not showing any evidence of high risk, you know, factors, and they have a platelet problem, you know. Promact is not a bad idea, and 31 patients compared with none in the placebo arm to get complete response. That's pretty impressive.
- There are other strategies for myelodysplastic syndrome, especially when you look, you're trying to decide. Does this patient have an aplastic anemia? Or is this Mds. And that's using our treatment that we would give to aplastic anemia atg and cyclosporine. This was a large multi-institutional retrospective study that looked at patients responses to atg and cyclospor
- cr rate. Isn't that great? But overall response is pretty impressive. And obviously, if you get that Cr, you have a pretty substantial improvement in overall survival.
- We can give low dose chemotherapy to these patients as well. But this kind of beyond the scope of this talk. So I'm going to move on.
- We're going to come back to our patient. We diagnosed her with Mds. We've told her that she's low risk. So we've staged her, and now we're going to talk about treatment. So you guys know that she has. Sf, 3 b. 1, she's deletion 20. Q. What's the next step to evaluate, and what we should give her
- has to do with that communication between the bone marrow and the illustrious kidneys.
- Well.
- so if the epo level is less than 500 we can give. Epo. Epo. In her is 720. She's Sf, 3 b. 1. She has ring sideroblasts. You guys have been paying attention. What's the next best treatment for her? Do I give her chemo? Do I give her Erythropoiet stimulating agent loose, Patricep? Or do I just send her to Hospice.
- Yeah.
- So we've spent a lot of time talking about low risk. Mds, and that's because the improvement that we've made in low risk. Mds is apparent, and we've actually made significant progress in that section.
- High risk. Mds is the next kind of portion of the talk, and it might not be as exciting as the prior talk. So if you have a high risk, Mds patient, remember they're hanging out over here.
- so they have a pretty terrible life expectancy. Your standard of care is hypomethylene agent. We're going to talk about that and stem cell transplant is the only curative therapy. So if you want to give your patient, meaningful life moving forward
- and and stem cells. Stem cell transplant can be done in older patients as well, because we use reduced intensity conditioning. So if you really want to give your patient, meaningful life, and they're healthy and and they can handle it. You know. Stem cell transplant is their best bet at long-term life.
- So this is our workhorse in Mds. And it's been our workhorse since 2,006. It's Azacitidine. It is a hypomethylene agent. Remember, we spent a lot of the talk before talking about the importance of epigenetic control and methylation. Well, this drug works by causing those epigenetic changes and allowing for cells to differentiate killing cells, bad cells as well with DNA damage.

- and in a phase 3. Clinical trial compared to supportive care or conventional care. Azacitidine beat out this 24 to 15 months. The problem is is that no Mds doctor can really get our patients to 24 months.
- And so you know, a lot of us, you know, are a little hard on this trial, and and we really, whenever we speak to our patients, we talk about, you know, on average a year and a half. Maybe that's kind of what I'm looking at with Azacitidine
- pretty terrible. It takes 4 to 6 months to work.
- And there's only about a 20% chance that you're going to get a complete response, which is the only meaningful response in Mds
- for survival.
- So not only that you're going to give them completely tank their bone marrow. So you're going to give them wheat, killer, and essentially kill all of their marrow.
- and you have low white cells, infection, malaise and bleeding for all of my colleagues in internal medicine subspecialties that help me with my patients that have significant cytopenias. Maybe they have a gi bleed. This is a shout out to you guys, we really appreciate you working with us. We don't live in an ideal world. But we really appreciate you guys thinking outside the box with us on service, constipation and nausea.
- And so Azacitidine has been kind of our workhorse and then exciting news. We get a new therapy in Mds. And not so exciting news. It's just Iv Oral version of an Iv drug that we get for Mds. It's okay, you know, oral decidabine instead of Zeridine. We can now keep our patients at home. They can take their drug at home.
- They're still going to come to the Infusion Center once or twice a week. They're still going to get blood transfusions, but it's a step in the right direction. This is a phase, one clinical phase, 2. Clinical trial that looked at Iv versus oral decidabine, and said, Yeah, they look pretty similar. You can use them interchangeably.
- So the only meaningful treatment for Mds is stem cell transplant. And you can see this is just a rick, because most of our patients are older, right. And so they're not going to be able to get a myeloblative stem cell transplant. But you can see that we do see a difference in survival with stem cell transplant.
- It can have a pretty high mortality rate, you know, upfront, as well as you know, within the 1st 3 years. But this is all we have. And so when we get our patients a response, or if we're really trying to improve their survival as a young patient, we're going to push for stem cell transplant. And we can change lives. We can get patients cured. We can get them more holidays with their families.
- more birthdays. So that's kind of what we're focused on as nds docs.
- This is this failure history of Azacitidine. So Azacitidine has been tested in a lot of phase, 3 trials, not just Azacitine pricinistat. It looks good at phase one and phase 2. And then we get to phase 3, and everybody's disappointed. Azacitine is extremely toxic, and if you add any kind of toxicity to that drug.
- you are going to get patients that can't tolerate it and have to discontinue the trial. And so this is kind of a sad part of the talk. We don't have really good chemotherapy options right now for patients with Mds. We had a really stinging result with Megrolimab not too long ago. And so this is kind of where we are at. Unfortunately.
- I titled this slide resiliency because we were so excited about Azacitine and Tanabaritone versus Azacitidine. It's a raw, raw inhibitor, and it's a targeted inhibitor. And unfortunately, November 12th 2024. This did not meet its primary endpoint.

- Again, nothing is beating monotherapy asap.
- but resilient optimism is a then, so we love the metaplex in acute myelo leukemia, and it has changed the lives of lots of elderly patients. We used to send all of our elderly patients out on a hospice if they couldn't tolerate intensive induction.
- and we now have a very effective therapy in those patients. The problem is, we don't know if it works in Mds. And everyone is waiting with bated breath
- for the phase 3 clinical trial with Azacitidine and Venetoclax. In my personal practice. If a patient has a blast percentage over 10%, I follow the Icc and I say, this patient is more likely to have acute myeloid leukemia.
- We code it Aml. And Mds. So all of the therapies that are available to my patients with acute myeloid leukemia that Mds patient can now get. And so that's my practice. I do add Venetoclax, especially the young patients who have excess blasts. We do not know if that's the right answer right now. But that's what we have
- a word on. Relapse. Refractory. Mds. We do have a success, Ivocinib. It's an idh one inhibitor, if you're thinking, idh! One sounds like a familiar enzyme, it is. It's from the Krebs cycle. So isocitrate dehydrogenase
- from your biochemical days and really Mds Aml. Hijacks that. And you can see that alpha-ketoglutarate, which is the product of Idh, gets reduced to 2 hydroxyglutarate it inhibits differentiation of the cell. And so if you block that, you can actually improve patients, blood counts, you can actually differentiate those bad cells. They die
- then. And so this is pretty exciting. We have this in Aml as well. And we've seen really fantastic results.
- Just like Aml, we saw fantastic result. 40% Cr rate time to Cr. Was 1.9 months Median Median cr duration at the publication
- was not determined. It was too long. And this is exciting right until you find out that only the idh mutations only positive about 5% of Mds patients. So we have a treatment. What we don't want to do is switch our chemotherapy backbone. We all do it because we feel bad. We don't have anything else to do for our patients.
- But really, guys relapsed refractory Mds needs a clinical trial. We need to be putting patients on trial for this entity.
- So in conclusions, we have nds which has a very progression. The majority of nds patients are older. You guys know now know why all those mutations that you're getting when you age.
- Mds is diagnosed by morphology and genetic review. It's staged very uniquely unlike other cancers, it's only staged with cytogenetics, molecular studies, and clinical staging, and we've made good progress in the treatment of our patients with low risk disease. We are still waiting for that breakthrough in the treatment of our high risk patients.
- So with that, I'd like to acknowledge everyone at Uva we have an incredible leukemia program, and obviously our Mds and Aml. Patients.
- I'll take questions.
- Thanks for that talk. I do have a question, Dr. Reid, with respect to your lenalidomide slide. I was hoping you could weigh in on like the mechanism of action for lenalidomide, if possible. But then, if we have an understanding for why like that? 5 Q. Deletion mutation and like? Why, that seems to work better or pair better, or the mechanism between?
- Because it has a lot of cellular biology that I don't uniquely understand.
- It has to do with ubiquination of proteins and degradation of proteins.

- Lenalidomide is an immunomodulator drug that we don't have great understanding of.
- and deletion. 5 Q. Has some kind of interaction. So the deletion of the 5 Q. Chromosome has some kind of interaction with a bunch of those DNA damage kind of proteins and interaction with ubiquitation. This is all to say that I took that slide out, and I'm sorry I'll get back to you on that answer.
- Yeah, it's it's it's more complicated than than I am not doing it justice.
- Thanks, Dr. Reed. So my question has to do with the earlier part of your talk. You mentioned some of the inherited sort of germline mutations that you can see with Mds. Is there any movement towards screening for these or thoughts about like. So we should be screening all of our young patients who are diagnosed with Mds patients who are in their forties or fifties, even their sixties for germline mutations.
- A lot of our germline mutations are caught on Ngs panel not all of them, but our myeloid panel is sent for all of our patients. We're in the transitioning of getting a new myeloid panel that has more of these mutations like Ddx 41. But I will refer young patients to our fantastic, clinical geneticist group to facilitate testing with younger patients with Aml and Mds.
- Great talk, Tim.
- my question is about thrombopoietin agonists, because I was very excited actually to see that portion of your talk.
- Or the question I have is, it seems that most of the patients who benefit from it aren't low risk, and most of the patients who really need to get it are high risk. And I think
- I'd be interested in your interpretation, too. Of do you think it'll ever get there? Because it seems like it's a
- question of risk, with transformation, not proof of transformation right? And there's no definitive proof. And this is all just digging back and looking at the safety analysis of these trials. Looking at who transformed, you know, the big Rami Blaston study is what was kind of hot whenever.
- a while ago, which was concerning for potential patients who were blasting off on Romney Plastin. And when they did further kind of thoughts into that, it seems like those patients had more
- probably had higher blast percentages that we're getting them on the blast. And so in a patient that's under 10%, you know, I might consider if they're low risk, if they're truly, you know, because you can blast under 10% if you're like 6 or 7 or whatever. Sometimes the Ipssm. And if you're meeting all the other criteria for low risk, sometimes there's still low risk, and so you can. I would I would think about it, and then I would give it, and then I would do a bone marrow
- like, maybe 2 or 3 months later. I have used it 3 times in practice. and I've had good results.
- Great talk, Dr. Reid. I had a question about in Covid, because I feel like the convenience of oral, decided Bean is so appealing, but
- I still feel like we see a lot of the parental hypomethylating agents still in practice. And I was curious what your thoughts were, because when we talk about quality of life having to have these patients come in monthly for a week. Seems like a big, the money thing. It's expensive, and insurance companies will
- cover it. But it's an additional expense to patients. Actually, with the iv shortage, we've actually tried a bit more mindful about getting it approved in our patients. I love to give it to these patients that I see as a consult. And then they're going to go to Southern Virginia.

- and they're going to see their local oncologist just for transfusion needs. But they're going to, just, you know, be able to take their pill at home.
- That's where I like to use it. But with the iv shortage. We've also been using a lot of subcutaneous injections of Aza not great over a long time, because these patients develop skin reactions knots in their stomach. It's kind of a miserable drug whenever you get it for a long term. But for the short term iv shortage we've kind of been using that and a combination of using
- oral and kobe just oral decided, we said, is your
- we call it Deck C in the in in the leukemia field.
- Hey, Danny? Thank you so much for this talk. I wonder if you can comment on the risk when you have a ship or Ccos to progress? Actually to Mds. And how do you monitor these patients? Is that something you do, or you defer that also to the primary care setting because you cannot
- monitor all of these patients. Hematologists should be monitoring this. I feel like and you know, Chip.
- depending on the risk of Chip, which, as you saw, we were, there was an older study that was published, I say older, but literally like last year, 2023 in the New England Journal of Medicine Evidence journal that looked at a clomocytopenia calculator and had a whole bunch of things
- platelet count Mcd, you know. Type of mutation. And you know, you could type all these things in. But if you didn't have a cytopenia associated with Chip, your
- risk of transformation, Mds. And leukemia is much lower. And so I feel like.
- I'm going to follow every ccus patient definitely, because you know, I think that they're more at risk. Chip also spans internal medicine. So Chip increases your cardiovascular risk. And so we do have. There are chip clinics in the nation. Dana Farber has one where they kind of co-manage hematology and cardiology. We've looked into, I think.
- doing a chip clinic at some point chips hard for us to find, because we really need people to refer Chip. We're not doing bone marrows and doing molecular studies on people who
- don't have abnormal counts. Right? So we're relying on the breast cancer Doc, that sends genetic testing. That finds this myeloid mutation they don't know what to do with. Or you know, this geneticist that's sending, testing, and they find something that they don't want don't know what to do with. It's harder to find Chip
- for hematologists. You really have to have good referral Ccos. We diagnose all the time, and ccus is challenging. But I was really excited to see that publication in blood, because it looks like splicing mutations. Platelet count, and the number of mutations really is what's driving most of the risk of transformation.
- I'm going to be using that stratification going forward for my clonal cytopenias.
- It's a tough conversation to have with patients, too, because that's not a cancer yet.
- that's appropriate to say, well, you don't have a cancer yet, but you do have cells that have made a decision to, you know or have been mutated because of some kind of environmental toxin or something that has led to this. You don't have dysplasia. You don't have clonal cytogenetic abnormalities that define Mds.
- We just have this molecular mutation. What are we going to do with it? And and those are tough conversations. But I find that the the factory analogy in my practice
- patients usually like that. I also like to use the instruction book analogy. So DNA is an instruction book because books everybody knows what a book is, and chromosome changes are like pages that are ripped out of the book, you know,

Ngs changes or molecular changes are kind of like misspellings or misprints or and patients. Really, I think you know, Jive, with that.

- thanks, guys.
- yeah, thanks. Thank you.