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A Novel Therapeutic Approach in Myeloid Malignancies: Targeting the Neddylation Pathway

Announcer:
Welcome to CME on ReachMD. This activity, entitled “A Novel Therapeutic Approach in Myeloid Malignancies: Targeting the Neddylation Pathway” is jointly provided by Albert Einstein College of Medicine, Montefiore Medical Center, and Spire Learning. It is also supported by an independent educational grant from Takeda Oncology.

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Dr. Caudle:
Managing symptoms and reducing disease burden are important goals when caring for patients with myelodysplastic syndromes, including chronic myelomonocytic leukemia, and delaying progression to acute myeloid leukemia is paramount. So, for patients who may be ineligible for more intensive therapies, how does targeting the neddylation pathway lead to the development of new therapies. This is CME on ReachMD and I’m your host, Dr. Jennifer Caudle, and with me today is Dr. Mikkael Sekeres, director of the leukemia program at the Cleveland Clinic Cancer Institute and Dr. Sarah Tinsley, a nurse practitioner in the malignant hematology division at the Moffitt Cancer Center in Tampa. Dr. Sekeres and Dr. Tinsley, welcome to you both.

Dr. Sekeres:
Thanks so much. It’s a pleasure to be here.

Dr. Tinsley:
Thank you. I’m happy to be here.

Dr. Caudle:
Starting with you Dr. Sekeres. Could you briefly define myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia for us?

Dr. Sekeres:
Absolutely. Myelodysplastic syndromes are actually a type of cancer. Cells in the bone marrow acquire genetic abnormalities that lead them to grow in an uncontrolled fashion and to grow abnormally. Myelodysplasia refers to myeloid cells that are bad-growing dysplastic. They’re a group of hematologic conditions characterized by chronic cytopenias and abnormal cell maturation. They’re actually considered by some to be the most common class of acquired bone marrow failure syndromes in adults, affecting approximately 4.5 per 100,000 U.S. citizens each year or about 20,000 new diagnoses per year in the United States. They have a clonal basis, as I mentioned. There is a genetic origin. It’s been defined in up to 95% of people diagnosed with myelodysplastic syndromes and they have the potential to ultimately evolve into acute myeloid leukemia. Chronic myelomonocytic leukemia is actually a combination of two different diagnoses. It includes myelodysplastic syndromes and also myeloproliferative neoplasms and its clinical manifestation reflects that. Approximately half of the people diagnosed with chronic myelomonocytic leukemia will have blood counts that will look for all the world like myelodysplastic syndromes. They’ll have cytopenias. They’ll have dysplasia in the bone marrow that they’ll have over 1,000 monocytes and that’s one of the sine qua nons of the diagnosis of CMML. The other half of patients with CMML will actually have a high white blood cell count and may look for all the world like other myeloproliferative neoplasms. These are also clonal with a very similar display of somatic and germline mutations as patients who have MDS and they also have the potential to evolve to acute myeloid

leukemia. Acute myeloid leukemia itself, of course, is a type of acute leukemia and when it's seen in older adults, which is common, it may have clinical manifestations that are similar to higher risk myelodysplastic syndromes or a higher risk chronic myelomonocytic leukemia.

Dr. Caudle:
And just as a quick follow-up to that, Dr. Sekeres, can you highlight the treatment options that are currently available?

Dr. Sekeres:
I sure can and unfortunately this will be quick because there aren't many of them. For myelodysplastic syndromes, there are only four agents that are approved by the FDA for the treatment of myelodysplastic syndrome. Two of them, azacitidine and decitabine, are often referred to as hypomethylating agents and are preferentially used in patients who have higher risk MDS or "lower risk" MDS but with multiple cytopenias. Lenalidomide is approved by the FDA for the treatment of transfusion-dependent lower risk MDS patients who have the deletion 5q abnormality and in those patients can be effective at increasing the hemoglobin. And most recently, luspatercept has been approved for lower risk transfusion dependent MDS patients who have ring sideroblasts or the somatic mutation that's associated with ring sideroblasts, SF3B1, or other spliceosome mutations. As I mentioned, the hypomethylating agents are more commonly used for patients who have higher risk MDS and the only curative approach we have for MDS is a hematopoietic cell transplantation. We often recommend that patients receive either azacitidine or decitabine en route to that transplant in case the transplant doesn't work out for them. Patients with chronic myelomonocytic leukemia, if it looks like MDS, are treated as if they have MDS with the same agents, azacitidine and decitabine, lenalidomide, erythropoiesis stimulating agents which we also use in lower risk MDS, and potentially luspatercept. For patients who have more of a myeloproliferative manifestation of CMML, we treat them as if they have myeloproliferative neoplasms. We sometimes will use hydroxyurea to lower the white blood cell count. Patients who have acute myeloid leukemia, particularly those who are older adults, have a real challenge with deciding what therapy to receive. Some may opt for intensive, aggressive, inpatient therapy with classic 7+3, seven days of cytarabine and three days of an anthracycline. They may opt for a conjoined version of 7+3 and CPX-351, particularly if they have a history of an antecedent bone marrow disorder, or they may opt for outpatient therapy with a hypomethylating agent-based approach, so, either azacitidine or decitabine alone for AML, or combined with a drug like venetoclax.

Dr. Caudle:
Thanks for breaking all of that down for us, Dr. Sekeres. Now, the following animation will illustrate how current therapy with inhibitors of DNA methyltransferase work to treat patients with these myeloid disorders. Let's watch.

Announcer:
Myeloproliferative neoplasms, including myelodysplastic syndrome, acute myeloid leukemia, and chronic myelomonocytic leukemia, are characterized by defects in hematopoietic stem cells and myeloid progenitor cells. DNA methyltransferases cause the aberrant DNA methylation of tumor suppressor genes which become hypermethylated and transcriptionally silent in some blood cancers. Here we see azacitidine target the aberrant methylation of DNA to reverse epigenetic silencing and reactivate tumor suppressor genes.

Dr. Caudle:
So, Dr. Tinsley, as a nurse practitioner, how do you work with patients to help them make decisions about intensive versus non-intensive therapy, and what are some tips for educating them about what to expect during treatment?

Dr. Tinsley:
Thank you. Oncology nurses, nurse practitioners, nurse navigators, and physician's assistants play a key role in communicating and educating patients and their families so that they can make informed decisions. We work as a team in meeting the needs of our patients diagnosed with these myeloid malignancies. Patients and their family members are typically overwhelmed at their first visit. Myeloid malignancies are unfamiliar terms for most individuals. A follow-up visit is usually scheduled for further discussions of their diagnosis and treatment. This is an excellent time to ask them, "Can you tell me what you understand about your illness and the treatments which were discussed?" The next question, which can occur at the same time or an alternate time, is "What are your goals with your current treatment?" You can offer resources and facilitate communication and assist with healthcare planning. Excellent resources for the patient and their caregivers are the Myelodysplastic Syndrome Foundation, the Leukemia and Lymphoma Society, and the Aplastic Anemia and MDS Foundation. Other resources geared more for healthcare providers that help improve communication and symptom management skills are the End of Life Nursing Education Consortium, known as ELNEC. There is also Vital Talk, which has an app that's free, to help lead the discussions with patients, and the Center to Advance Palliative Care, known as CAPC. Another well-known resource for nurses is the Oncology Nursing Society, and one for advanced practice providers is JADPRO or APSHO, working with patients and families to understand and plan for potential long-term adverse effects associated with treatment. Once the best treatment is chosen, we tailor the discussion to the treatment. For our myeloid malignancies, the focus is on the complete blood count really and managing the consequences of cytopenias. We want to keep them safe and febrile neutropenia instructions are paramount. Another

common problem is the bleeding risk associated with thrombocytopenia. A careful review of their medication list is needed to discuss medications that increase their risk for bleeding and eliminating those medications during periods of severe thrombocytopenia if possible. You also want to discuss over-the-counter medications that are commonly utilized, including the non-steroidal anti-inflammatory group, so that you can instruct them not to take those during periods of thrombocytopenia. Transfusions with both packed red blood cells and platelets are very common and the thresholds that we use for transfusion are needed to be discussed and consent obtained. Discussions with patients provide an opportunity to make decisions based on assessment of quality of life and really you want to align their treatment with their choices and their goals, especially our older patients. And really to better align treatments with goals, you really have to know your patient. This takes extra time and a focus on what matters most to the patient. Some of our patients will want to live as long as possible, even if this means compromising their quality of life, while others want to focus on comfort and improvement in quality of life.

Dr. Caudle:
Considering the current available therapeutic regimens, Dr. Sekeres, can you tell us about the toxicities associated with them, particularly in the older patient population, and share some management strategies?

Dr. Sekeres:
Sure, well let's start with older adults who have acute myeloid leukemia. If they choose aggressive inpatient therapy, then we're talking about a four-to-six-week hospital stay, a risk of therapy-related mortality that may be as high as 20% in patients who have other comorbidities, and obvious toxicities of nausea, drop in blood counts, infections, and bleeding risk. So, it's a really tough decision for patients to make whether they're going to go down that route or if they're going to opt instead for outpatient therapy. Outpatient therapy for somebody who has acute myeloid leukemia, as I mentioned, is hypomethylating agent-based, which has them coming into a treatment center for seven days out of the month. Some drop in blood counts, but not nearly the risk of death that they would have in the inpatient setting. This decision is so challenging, in fact, that we have developed guidelines for practitioners to use through the American Society of Hematology on how to have these discussions and how to make these decisions with older patients who have acute myeloid leukemia that are now out in the journal, Blood Advances. For patients who have myeloid dysplastic syndromes, a choice of hypomethylating agents is similar to what it would be for patients who have acute myeloid leukemia with a drop in blood counts, frequent visits to a treatment center, and also a lot of my patients complain about fatigue as well as nausea. We're able to mitigate the nausea with very good antiemetics, but the fatigue may be either a side effect of the chemotherapy itself or, frankly, of the number of times someone has to get into a car and drive to a treatment center every single month. These side effects are similar for patients who have chronic myelomonocytic leukemia, particularly those who take the hypomethylating agents, whereas the side effects of taking a pill like hydroxyurea to lower the white blood cell count are actually quite minimal. One of the things we try to do when we're helping patients make this decision about how aggressive to be in their treatment is instead of focusing on an absolute age, because, quite frankly, someone who's older can have a younger person's acute myeloid leukemia, someone who's younger can have an older person's acute myeloid leukemia, we start to think about measures of frailty and "fitness" by assessing other things like comorbidities, functional status, emotional health, cognitive performance, the number of other medications somebody is on, their social supports to help them get through this treatment, and the presence of other geriatric syndromes or to engage in geriatric assessments.

Dr. Caudle:
As we'd mentioned in the beginning of this program, Dr. Sekeres, the neddylation pathway is leading to the development of some novel treatments. Can you explain this cellular pathway for us?

Dr. Sekeres:
Sure thing. Well, neddylation is a post translational modification that adds a ubiquitin-like protein known as NEDD8 to other cellular proteins that modulates a number of processes including tumor genesis, cell growth. Protein neddylation is overactivated in a number of cancers making it a particularly interesting therapeutic target. Thus, the NEDD8 activating enzyme inhibitor, pevonedistat, is actually a neddylation enzyme inhibitor, that's been developed. One of the reasons it reached this stage, and a lot of drugs never make it to even animal trials never mind human trials, is that it exerts significant anti-cancer effects mainly by triggering cell apoptosis, senescence, and autophagy. Neddylation enzyme in – inhibition can also influence components of the tumor microenvironment, including immune cells, cancer-associated fibroblasts, cancer-associated endothelial cells, and other factors, all of which participate in tumor genesis.

Dr. Caudle:
For those of you who are just tuning in, this is CME on ReachMD. I'm your host, Dr. Jennifer Caudle, and together with Dr. Mikkael Sekeres and Dr. Sarah Tinsley, we're talking about managing patients with myeloid malignancies and emerging therapies targeting the neddylation pathway. Now, let's turn our attention to the following animation, which illustrates how the neddylation pathway works within the cell and, more specifically, how pevonedistat acts in the treatment of advanced acute myeloid leukemia as well as myelodysplastic syndrome.

Announcer:
The neddylation cascade is catalyzed by three NEDD8-specific enzymes, E1 NEDD8-activating enzyme (NAE), E2-conjugating enzyme, and cullin-RING ubiquitin (E3) ligases. Here we see the ubiquitin-like molecule NEDD8 activated by E1/NAE, which is then transferred to E2, and conjugated to substrates, such as the tumor suppressor p21, by the culling-RING ubiquitin (E3) ligases. Overactivation of protein neddylation leads to degradation of tumor suppressors, and facilitates cancer cell growth and survival.

Pevonedistat is a small-molecule inhibitor of the NEDD8-activating enzyme which inactivates the first step of the neddylation cascade. It has shown activity as both monotherapy and in combination with azacitidine in advanced acute myeloid leukemia as well as myelodysplastic syndrome.

Dr. Caudle:
So, Dr. Sekeres, can you tell us a bit about the clinical trials that are evaluating pevonedistat for myeloid malignancies?

Dr. Sekeres:
Sure, happy to. Uh, there was a phase Ib study that was published a couple of years ago in the March 2018 issue of Blood by Ronan Swords and colleagues based on promising phase I results for pevonedistat as a single agent in relapse and refractory acute myeloid leukemia and on promising pre-clinical studies when it was combined with the hypomethylating agent, azacitidine, that pevonedistat-azacitidine combination was evaluated in this early phase study of 64 patients. In this study, 50% of patients actually responded to the drug with 20 complete remissions, 5 complete remissions with incomplete peripheral count recovery, and 7 partial remissions with a median duration of response that was 8.3 months, which is actually considered pretty good for a relapse refractory setting in acute myeloid leukemia. For the 23 patients who received six cycles of therapy or more, the overall response rate was quite generous at 83%. And this was the provocative study that led to the suggestion that the combination of pevonedistat and azacitidine could be a viable therapeutic option for patients with higher risk myelodysplastic syndromes, acute myeloid leukemia in the upfront setting, and patients with chronic myelomonocytic leukemia. So, the combination has been evaluated in phase II and phase III trials. We recently presented the results of the phase two study at ASCO in which 120 patients with higher risk MDS, chronic myelomonocytic leukemia, and low blast count myeloid leukemia were randomized to receive azacitidine monotherapy or the combination of azacitidine and pevonedistat. The primary endpoint of this study was event-free survival and actually event-free survival for the combination was a median of 21 months versus only 16.6 months for patients who received azacitidine monotherapy with a trend towards significance. This study was empowered on overall survival, but numerically overall survival was also improved at 22 months for the combination versus 19 months for azacitidine monotherapy. The group of patients who had higher risk myelodysplastic syndromes, the median event-free survival and overall survival for the combination versus azacitidine monotherapy was 20 versus 15 months, which was a significant difference, and 24 versus 19 months for overall survival. In a follow-up phase 3 trial the frontline combination is being compared to azacitidine in patients with, higher risk MDS, chronic myelomonocytic leukemia, and low blast count acute myeloid leukemia, patients who are often considered ineligible for transplantation. A key objective of the PANTHER studies to compare survival of patients treated with the combination of pevonedistat and azacitidine after failure of hypomethylating agents to historical survival of four and a half to six months in this patient population again in patients who are ineligible for transplantation. There are a number of additional trials that are assessing the combination of pevonedistat and azacitidine including in patients with newly diagnosed acute myeloid leukemia who are not eligible for standard intensive induction therapy or transplantation, patients with relapsed refractory acute myeloid leukemia, and finally as post-transplant maintenance therapy, uh, in patients who, uh, don't achieve a remission with acute myeloid leukemia. patients who have the non-proliferative type of chronic myelomonocytic leukemia, higher risk myelodysplastic syndromes, low blast count acute myeloid leukemia. There is also a triple combination that's being explored, now adding venetoclax to the mix of pevonedistat and azacitidine in a phase I/II trial in patients with newly diagnosed acute myeloid leukemia and another phase I/II trial evaluating the combination of pevonedistat, cytarabine, and idarubicin in patients with previously untreated acute myeloid leukemia arising from an antecedent myelodysplastic syndrome or an acute myeloid leukemia with myeloid dysplasia-related changes or in therapy-related acute myeloid leukemia.

Dr. Caudle:
So, Dr. Sekeres, can you discuss the clinical implications of neddylating activation inhibitors for eligible patients with higher risk myelodysplastic syndromes, including chronic myelomonocytic leukemia as well as acute myeloid leukemia, and how you discuss options with patients who may be eligible for a clinical trial of investigational therapy?

Dr. Sekeres:
So, as I mentioned earlier, hypomethylating agents as monotherapy are a standard treatment for patients with myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia, but they're by no means a panacea. They aren't curative. Typical response durations to azacitidine alone in somebody with myelodysplastic syndrome is about 12 to 15 months. In somebody who has acute myeloid leukemia, that may be a median duration of response of maybe about 8 to 10 months. So, there's obvious

opportunities for improvement and a lot of us are veering more towards combination therapies to try to see if we can improve on those basic outcomes to hypomethylating agent monotherapy. So, I talk about the result of azacitidine monotherapy with my patients and then introduce the option of an investigational therapy and one of the ways I talk about this with one of my patients is to say, it's not as if, first of all, I'm giving you a drug that's been tried in lab rats and congratulations, you're next, and secondly, that it's not as if I'm giving them no therapy. At the very least, they're getting the standard therapy but they're getting the standard therapy plus an investigational therapy that may have the potential to introduce more side effects but also may have the potential to improve their outcome.

Dr. Caudle:
Okay, and finally, Dr. Tinsley, how do you talk to your patients about clinical trials and the decision to enter a clinical trial?

Dr. Tinsley:
That's an excellent question and it comes up often. We have several clinical trials at Moffitt. The first question I ask the patient is, "Would you be interested in participating in a clinical trial if available?" The next step is finding the right trial for that patient. All of the clinical trials have inclusion criteria and exclusion criteria. So, we have to find the trial that matches their diagnosis and that they don't have any of the exclusion criteria. If there's not an available trial at Moffitt, then I help them look for other trials if they're really motivated for continuing to receive treatment, and a good place for that is at clinicaltrials.gov, and again we must look at the fitness level of the patient and their comorbidities which make them ineligible for participating in many of the clinical trials, especially our older patients who have multiple comorbidities. Other considerations are the distance from the institution that would be an obstacle for participating in the clinical trial and how many times a week they have to come and how many bone marrow biopsies that have to be performed. That all factors into whether or not they're interested in participating in one trial or another. Uh, some of our clinical trials provide support for lodging if that's an obstacle, so, that is reviewed with them once a trial is decided on and this is an excellent time for re – revisiting the patient's goals of care.

Dr. Caudle:
I would like to ask both of you, how has the COVID-19 pandemic impacted the care of patients with myelodysplastic syndromes and other myeloid malignancies? Dr. Sekeres, why don't you start us off?

Dr. Sekeres:
Oh, boy. I'll tell you, this has been a heck of a challenge for all of us in healthcare. Not only worrying about our patients catching COVID-19 but also our – our colleagues, our family, and frankly ourselves. What we've recommended both at Cleveland Clinic and also as part of formal guidelines that we've written, that are through the American Society of Hematology, is that, patients who have higher risk MDS or who have acute myeloid leukemia or a more advanced myelomonocytic leukemia should not delay therapy because of the COVID pandemic. They have a diagnosis that is arguably scarier and more deadly than, uh, COVID would be to them. So, we've recommended that those patients continue to receive hypomethylating agent-based therapy on schedule without delays. Now, somebody who has a lower risk MDS or one who doesn't have as advanced chronic myelomonocytic leukemia may be able to delay starting therapy if his or her blood counts are preserved. But if that person already is coming into a treatment center and receiving blood and platelet transfusions regularly, then it's really up to us to try to manage that disease and hopefully minimize the number of times they actually have to come into a treatment center to receive those transfusions. There are two recent studies from China that have looked at COVID-19 in patients with cancer and a couple of studies that have now come out of the U.S. that indicate that people who have these sort of hematologic conditions aren't necessarily more susceptible to catching COVID, but if they get COVID, they're much more likely, three to five times as likely as other cancer patients or the general population, to get extremely sick from COVID. So, I do review COVID precautions with my patients during every visit, and although states are opening up and the activities we can all participate in, I've advised my patients to remain socially isolated until the pandemic starts to resolve or we have a vaccine.

Dr. Caudle:
Thank you, Dr. Sekeres. Dr. Tinsley, same question for you. From the nurse practitioner perspective, how has the COVID-19 pandemic impacted care of your patients with these types of myeloid malignancies?

Dr. Tinsley:
It is very tough these days. I would say we have performed more telehealth visits. The patients have come in, had their labs drawn, and then go back to their car and then I have a visit with them and then we'll bring them into the transfusion unit if they need blood or platelets and I just go over what symptoms they're having and seeing, you know, how are they doing? How are they handling things emotionally? And for our acute myeloid leukemia patients, COVID-19 is forcing the patients to reevaluate really what is most important to them. I've had several patients that chose an outpatient-based therapy primarily because of the limits placed on visitors who are coming in for a four-to-six-week hospitalization. Some of the restrictions are that they, at our institution, were that they could not have another member of their family with them, so, there were no visitors. And this resulted in patients choosing an outpatient-based therapy because they didn't wanna be separated from their loved ones. So, they changed their choice of treatment because of the value that

they placed on the close support of family and friends during this COVID-19.

Dr. Caudle:
That was all very helpful but now we're unfortunately at the end of today's discussion. So, I'd like to thank Dr. Mikkael Sekeres and Dr. Sarah Tinsley for joining me to review this very important information for clinicians who manage patients with myeloid malignancies. It was great speaking with you both.

Dr. Sekeres:
Thanks so much, you too.

Dr. Tinsley:
Thank you.

Announcer:
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