Angie Onofre: This is a pre-recorded presentation, so the presenter will not be taking any questions. However, all questions asked during the live presentation, along with answers, are included at the end of this presentation. To learn more about our upcoming patient and family conferences in your area, please visit AAMDS.org/conferences. To view other recorded presentations or to register for other live online learning events, please visit AAMDS.org/learn.

Welcome to our live webinar titled *What is Secondary MDS? Everything You Need To Know*. Thank you for joining us. My name is Angie Onofre, director of patient programs at AAMDSIF, and I'll be moderating the presentation today. As we get started, I would like to acknowledge Celgene Corporation for providing an educational grant to help support this webinar program. Today's presenter is Dr. Alison Walker. Dr. Walker is currently an assistant professor in the Division of Hematology at the Ohio State University. Her clinical practice includes the care of patients with myeloid malignancies, specifically acute myeloid leukemia, also known as AML, and myelodysplastic syndromes, also known as MDS. Her research is centered around drug developments for patients with both of these diseases and spends much of her time developing and enrolling patients to early-phase clinical trials. Dr. Walker earned her medical degree at the University of Rochester and served her residency and fellowship in hematology and oncology there, as well. It is my pleasure to welcome Dr. Walker.

Dr. Alison Walker: Thank you very much. I would like to thank the foundation for the opportunity to speak to people in this format. I think it's a great way to be able to disseminate information, and hopefully, those of you that are listening will find that the things that we talk about might help to make this complicated subtype of MDS a little bit more clear, so we'll go ahead and get started. So there are four learning objectives that I would like to get across today. The first one is to understand the difference between primary and secondary MDS. I also hope that you'll be able to understand the difference between the two general categories of secondary MDS, as well as identify disease characteristics that determine why your doctor makes a specific treatment choice, as well as your likelihood of response. Finally, I would like to suggest ways to perhaps work with our medical team in order to achieve your treatment goals.

So very briefly, I'll just start by reviewing what myelodysplastic syndromes, or MDS, are. So, in summary, they are a very heterogeneous group of blood disorders characterized by both low blood counts and the potential to transform into acute myeloid

leukemia. The incidence of MDS in the United States is about 5 per 100,000 people per year, and we know that as our population is aging, there will be more patients who are diagnosed with this disorder. It's much less common in those who are less than 40 years of age, although I personally have patients in their 30's with a diagnosis of MDS, and it is certainly more common in those patients who are over the age of 70. In fact, once you reach the age of 70, the incidence increases to about 30 patients per 100,000 people.

Given that myelodysplastic syndromes are very heterogeneous, the clinical course for patients can vary from being very indolent, so someone, for example, who has only mild anemia and really no other blood count abnormalities, no need for transfusions, no need for chemotherapy can vary to someone who has actually very aggressive disease who may even require a bone marrow transplant. Despite this variability within this general group, there appears to be a shared or what we would call a common mechanism to the development of this disease, at least as best as we can tell now. There appears to be an expanded growth of a stem cell within the bone marrow that has somehow required genetic mutations, and now we're learning, particularly in the past few years, that the type of mutation that is present will actually contribute to the characteristics of the disease in an individual patient. I really do think that our understanding of this basic pathophysiology will ultimately help us to develop better treatments and to tailor treatments more appropriately for patients.

So the most important prognostic factors for patients with MDS are really three different things. The first is the percentage of blasts in the bone marrow, and we know that the more blasts in the bone marrow the more aggressive someone's disease. We also know that the presence of very specific chromosomal abnormalities, or cytogenetic changes they're sometimes called, is also important, and finally, the extent or the depth of someone's blood count, so how anemic are they, how low are their platelet counts, how low are their white blood cell counts? As doctors, we look at the IPSS and the R-IPSS, which are abbreviations for scoring systems that actually help us to calculate a score based on these three different factors that help us to determine prognosis, and then also inform what might be the best treatment choice at the time of diagnosis. These scores were developed based on observations from two particular clinical trials that looked at large populations of patients with MDS, and it's important to note that those trials did not include patients with secondary MDS, and so even though we will often use these specific scores in discussing for a patient, it doesn't

necessarily represent them completely.

So given that we're going to be talking about chromosomal abnormalities in depth throughout the course of the talk, I just wanted to show this picture, which is actually what we look at in the pathology lab. This is a formal karyotype. These are actual chromosomes. You see it's listed 1 through 22, and then you have the sex chromosomes, which are at the bottom, the X and Y, and the pathologist will actually look at these squiggly lines and be able to tell if every part of chromosome 5 is there, or if every part of chromosome 7 is there, or if there's an extra chromosome. So, when your doctor talks about, "Oh, you have a deletion 5Q or an abnormality of chromosome 5," they're actually talking about something like this, which has been reviewed by doctors, pathologists who specialize in this.

I would just like to take a moment and show here where we have a chromosome – I'm just going to try to use this arrow here – so this is actually a schematic of what those squiggly lines looked at. Actually, when you unravel that, it forms or is actually made of your DNA, and this is what that looks like at sort of the microscopic level, and so I just wanted to show that because we'll be talking about, with respect to secondary MDS, chromosome changes, as well as their causes, which affect the DNA, and so I just wanted to take a moment for that. So we know that there are risk factors for developing MDS, and probably the most important or the most common is really advanced age. You'll remember that I had mentioned that MDS is more common over the age of 70 and the incidence, or in other words, the number of patients that are diagnosed with MDS, increases as people reach 70 years or older. But we also know that there are other things that are risk factors, including exposure to prolonged or high levels of benzene, radiation treatment and treatment with chemotherapy agents.

We know environmental exposures like cigarette smoke likely contribute. There's probably not as strong a link with cigarette smoking and MDS as there is, for example, with cigarette smoking and lung cancer. We also know that there are inherited bone marrow failure syndromes, something, for example, called Fanconi Anemia, and this is typically something that's diagnosed in kids. Typically, by the time someone is an adult, a diagnosis of an inherited bone marrow failure syndrome would already have been made. I can tell you, in my training when I was coming through my fellowship, we weren't as clear about the role of what we call now familial MDS, or inherited risks for MDS. Just like there are inherited risks, for example, for breast cancer, we're discovering

now that about ten percent of patients with MDS can have some sort of a familial disorder. One of the genes that are often mutated in this is a gene called GATA2. So we also know that the presence or absence of identifiable risk factors will determine whether a patient has primary or secondary MDS, and that whether they have one or the other will help to determine the final treatment plan, as well as the overall prognosis.

So right now, I would like to talk about the differences between primary and secondary MDS. So primary MDS is also called *de novo*, which is Latin for "from the new" so this is when MDS happens completely out of the blue and there have been no identifiable risk factors for the development of the disease, whereas secondary MDS is MDS that develops after either a prior blood disorder, such as essential thrombocytosis, polycythemia vera, or myelofibrosis. Those are three bone marrow disorders that actually cause a little bit of the opposite problem. In essential thrombocytosis, your platelets are very, very high. They can even be 1 million. In polycythemia vera, you have too many red blood cells, and so you can actually have a hemoglobin level of 17, 18, 19, 20, and then in myelofibrosis, those patients actually have scarring in their bone marrow that prevents some of the normal blood production, and so they can actually have a little bit of a higher white blood cell count but could also have some low blood counts. So those are different disorders from MDS but they are clearly bone marrow problems that can turn into MDS.

Secondary MDS is also MDS that develops after exposure to chemotherapy, radiation, or immune therapy. For example, for patients with a history of Crohn's disease or, for example, psoriasis, other disorders where oral chemotherapy like azathioprine, that can be given for diseases that are immune-related, and so that can also lead to the development of MDS. Secondary MDS does not include patients who have been exposed to some type of an environmental exposure like benzene. So, when you look at the whole pie of patients with MDS, those with primary or MDS that just comes out of the blue without any identifiable risk factor, they really make up the majority of patients, and actually probably about 80 to 85 percent, while secondary MDS or MDS from prior exposure to chemotherapy or radiation or having a prior problem is much less common, probably about five to ten percent. Then, familial MDS, that actually makes up less than two percent according to some older studies, but I think that that number will change as we learn more about these inherited familial problems. So now I would like to focus more on secondary MDS specifically.

So again, MDS following a prior blood disorder, whether that be polycythemia vera, essential thrombocytosis, or primary myelofibrosis, that's one subtype of secondary MDS, and then the second subtype of secondary MDS, so there are really two types all together, is those following prior chemotherapy or radiation therapy, as I mentioned. According to the WHO, which is a group that comes up with how we name different diseases and malignancies, has now called this particular subtype of MDS therapy-related myeloid neoplasms, so a much longer, fancier word than just secondary MDS, and so that includes both MDS and acute myeloid leukemia, as long as it's come from some or is felt to have arisen after some prior chemotherapy or radiation therapy treatment.

What's interesting is that the number of patients with therapy-related diseases, whether that be MDS or acute leukemia, is likely going to increase, and in fact, they think that by 2022, there will be 18 million cancer survivors. But chances are that given all of the new treatments and therapies, there are going to be more people who are living longer after their diagnosis of a cancer that they could be more at risk for something like this happen. The majority of MDS that is secondary occurs in patients who have had actually a prior solid tumor malignancy, about 70 percent of patients with secondary MDS have had that. Again, this likely reflects how patients with these types of cancers are living much longer. There are patients with a prior blood cancer, about 30 percent or so, who also can go on to develop MDS, and that would be patients who have Hodgkin's lymphoma or multiple myeloma which, again, are both types of blood cancers.

So the question might be why would chemotherapy or radiation lead to the development of MDS? There are a few different theories that people think about. First, could there be some initiating mutational event or series of mutations that directly cause the bone marrow stem cells to go awry because of the radiation or chemotherapy that they're exposed to? We talked a little bit at the beginning about the role of mutations going or happening within stem cells and ultimately leading to MDS. Another possible theory is that patients have some baseline susceptibility to the development of mutations within the bone marrow stem cells if they get exposed to radiation or chemotherapy. So it's not that they have the mutation but they're just at higher risk for developing a mutation that will lead to MDS once they get exposed to radiation or chemotherapy. A third possibility is that patients were already at risk to develop MDS even before they had received radiation or

chemotherapy, and finally, of course there's always the possibility of chance, just having bad luck, unfortunately.

So how do we explain these theories? When we look at Theory 1, the fact that mutations within the bone marrow occur only because of the exposure to the chemotherapy or radiation, and we know this to be true or partially true because there are very clear identified chromosomal changes that specifically occur at distinct time points following exposure to specific types of chemotherapy, so it's not all chemotherapy but rather specific types. There are two different groups, a group called alkylating agents and a group called topoisomerase II inhibitors. So talking briefly about each of these, alkylating agents were actually one of the very earliest classes of drugs used to treat cancer, and not just blood cancers, really all cancers. The reason why is because they target one of the greatest weaknesses of a cancer cell. They specifically attack the DNA structure causing it to break, which then prevents the cell from being able to divide and replicate. When a cell, even in a normal cell, when you're not able to remake your DNA and to grow, you do die, and so that's been the way that these agents, and other chemotherapy drugs, really try to target cancer.

Now, these alkylating agents have been used in many types of cancers, including lung, ovarian, brain, and breast cancer, and even in lymphoma and leukemia, and so there are a number of classes of drugs within this group. I think the ones that are common and that patients would be exposed to, for example, would be cyclophosphamide, which is a very common treatment as a frontline therapy for patients with breast cancer; chlorambucil is one of the most common chemotherapy drugs that's given for patients with the most common type of chronic leukemia called CLL; and melphalan. Melphalan is actually one of the main therapies for patients with multiple myeloma. Busulfan is used as part of chemotherapy regimens for patients who are receiving what we call autologous transplants for the treatment of lymphoma or Hodgkin's disease that's relapsed. Temozolomide is one of the more effective chemotherapies for patients with brain cancer, actually, and so these are common drugs that are given frequently to patients.

So what they discovered or what's been observed with alkylating agents is that there are several shared disease characteristics in patients who develop MDS after exposure to one of these drugs that I mention on the previous slide. Typically, they develop their MDS three to ten years after exposure to the chemotherapy agent, so it's not something that happens immediately, and then also, they

frequently have abnormal changes in chromosomes 5 and 7. So one of the very first slides that I showed that showed all the different chromosomes, the pathologist looking at that is able to see if there are changes within specifically chromosome 5 or 7 that would go along and support a diagnosis of a secondary leukemia. Frequently, there's also a loss of protein p53, and the role of p53 is that it helps your cell to prevent the development of cancer, so in another way of thinking of that, p53 is on your side. p53 goes around your cell and tries to squash any sort of thing that's going to make your cell go to the bad side and to become cancerous. So, when you don't have p53 there, that would be something that allows the cell to evolve and to become cancerous. We also know, again, that patients who develop MDS after radiation or treatment with azathioprine also have similar disease characteristics to patients who have been exposed to alkylating agents.

As far as topoisomerase II inhibitors, you'll remember from that second slide that I showed after the pictures of the chromosomes how the DNA was structured, it's put together much like a spiral staircase, and there are many different enzymes that work to put everything together. As I said, anything that can prevent a cell from being able to make its DNA normally and function is going to cause it to die, and so topoisomerase enzymes are very important for being able to make DNA. So these drugs, which inhibit this enzyme, prevent the cell from forming the DNA and that leads to cell death. So there are two specific classes of topoisomerase inhibitors − anthracyclines followed by epipodophyllotoxins. That's a mouthful. With respect to the anthracyclines, daunorubicin, which, again, is also one of the most common drugs used for patients who have acute leukemia, acute myeloid leukemia, but doxorubicin is used in patients that have breast cancer, and also it's a very common treatment for that cancer. Etoposide is used for a lot of different cancers, including lymphomas as well as lung cancer.

So we know that there are also several shared disease characteristics in patients who develop MDS after exposure to a topoisomerase II inhibitor. In contrast to alkylating agents, patients who have been exposed to a topoisomerase II inhibitor have a relatively short latency until they develop MDS, so that can be as short as a few months to about two years, and they usually causes changes somehow within chromosome 11. So this is just a slide to show us, for example, a dividing cancer cell, and that these are sort of the chromosomes here, these X's, that are then unraveled into the DNA, and we see here that topoisomerase inhibitors are working here to prevent the DNA from connecting, and then

alkylating agents are working here to prevent the joining and permanent replication within the cell.

So I would just like to summarize briefly what we've just discussed. So first, secondary MDS occurs when MDS is diagnosed after a prior blood disorder or after exposure to prior chemotherapy or radiation therapy for a separate cancer. Second, there are more patients who develop MDS out of the blue, something called primary MDS, as compared to those who develop MDS after chemotherapy or radiation. Secondary MDS that occurs after exposure to prior chemotherapy or radiation therapy is called a therapy-related myeloid neoplasm. Further, one theory as to why this occurs is that radiation or chemotherapy directly cause mutations within blood cells, and there are two classes of chemotherapy agents that have been implicated thus far, each associated with a specific time to the development of MDS, and specific chromosome changes.

So what about the other theories? What do we have to explain that? So Theory 2, the fact that there are some patients that are more susceptible to developing MDS in general, this refers to inherited cancer susceptibility, so for example BRCA1/2 are involved in DNA repair pathways, so trying to fix DNA after there's been some damage. There are other proteins, as well, that are important for maintaining the integrity of DNA, and so if there is some inherited or known susceptibility that you're not able to do that, you could be more susceptible to MDS. Another theory is that there are some patients who are more susceptible to developing mutations after exposure to chemotherapy or radiation as compared to others. More specifically, this actually goes to the idea that people could have different abilities to metabolize and break down chemotherapy drugs, which allows for byproducts and toxins to build up in the body rather than being eliminated, and could that somehow lead to exposure and damage to DNA. We can also see an increase in free radicals, which really can be a byproduct of chemical reactions in the body as your body is metabolizing drugs, and that somehow that can cause damage to the bone marrow.

So what is the prognosis of patients with a therapy-related MDS? Perhaps in one of the best and largest studies looking at this was actually that of 306 patients who had therapy-related MDS and acute leukemia. This was done at the University of Chicago, and they looked at 220 patients with myelodysplastic syndrome, and what they found was that younger patients tended to have a longer interval until the diagnosis of MDS, and that patients who had a non-cancer diagnosis had a longer time to diagnosis of MDS. So

that would include patients who were being followed or being treated for some sort of autoimmune disorder and had received chemotherapy and then went on to develop MDS. What was most interesting from the study, and also confirms the importance of how exposure causes these chromosomal changes and that that plays a role, is that more than 90 percent of the patients had some type of chromosomal abnormality.

The median overall survival for this particular groups of patients was about 8.6 months. Again, the chromosomal abnormalities that were present played a very important role. It was clear that the type of chromosome change that you had would impact someone's overall survival. For example, patients who had abnormalities of both chromosome 5 and 7 had the shortest median survival, which was about five months. For those that only had an abnormality of chromosome 5, their survival was a bit better at seven months. Those with only an abnormality of chromosome 7 had a median survival of nine months, and for those with no other chromosomal abnormalities, their median survival was longer at 11 months. Again, the median is that middle point, and that means that 50 percent of patients will have done better than that, and 50 percent of patients had done worse, so it's not necessarily an average of how long the entire group would live when they had those specific changes or were in those specific categories.

When they looked a these patients, they found that the most common solid tumor cancer was actually breast cancer, and one could argue that that actually is probably representative of the more common cancers being breast, for example, in women, although there were also patients who had ovary cancer, prostate cancer, lung cancer, and cervical cancer. Another factor that might be considered in the fact that more of the patients had breast cancer was that breast cancer patients tend to live longer, for example, than those who have very advanced lung cancer or very advanced ovarian cancer, and so that could be a factor of they haven't had time to develop any MDS because, unfortunately, they've passed away from, or rather due to their primary cancer. Again, similarly to what I mentioned before, the most common blood cancers were actually Hodgkin and Non-Hodgkin's lymphoma. Of note, they did include patients who had, or they did see MDS happening in patients who had had a diagnosis of multiple myeloma, and then there were a smattering of other one or two patients with other types of blood cancers, as well.

So this is a graph that actually looks at and reports the survival results that I mentioned before. I guess my pointer wasn't working

earlier. I'm sorry about that. There we go. It's back. So the patients in black here actually had the best survival, but what we noticed, with this being years on this axis and the percent of people that are alive, unfortunately we see that 50 percent, if you go to that point there, 50 percent of patients really within less than a year have, unfortunately, passed away, and so their survival is shorter. Let me see if I can get that – okay. Then, again, looking similarly at these curves, just looking at the group all together, it shows that most patients within this first year of time have succumbed to aggressive disease.

So looking at why their survival seems to be much shorter than those, for example, of patients who have primary or MDS that occurs out of the blue, the authors suggest that perhaps it has to do with the fact that they still have their original malignancy, or their first cancer, which made it difficult to treat their MDS. So, for example, someone who had active breast cancer, who needed to have surgery or chemotherapy or radiation for that, would not have been able to undergo treatment for their MDS; those two things would conflict. Another possibility is that their could be some organ dysfunction from the prior chemotherapies that they had gotten for their first cancer, so some of the chemotherapy agents that I mentioned can cause damage to heart-pumping function, and that could be affected. Sometimes chemotherapy can damage the kidneys, and that could be important, as well. Then, finally, we know that patients who are receiving chemotherapy for long periods of time can become immunocompromised or more at risk for the development of infections and complications, and so we think that perhaps that could be a reason for why there seems to be a lower survival for patients with this type of MDS.

So given that breast cancer was associated, at least in that particular study, with the highest number of patients who had MDS, that's obviously a concern, both for patients who provide care to breast cancer patients, as well as the patients themselves, and so there have been a number of studies that have looked at and tried to identify this. I think perhaps where this has become most to light, of course, is with Robin Roberts. She's done so much to increase knowledge and awareness of MDS, but she is an example of someone who was diagnosed and treated very appropriately for her diagnosis of breast cancer, and then, five years later, developed MDS and ultimately underwent a bone marrow transplant from her sister as part of her treatment. So there have been a number of studies that have tried to understand why patients with breast cancer, why that's more common, is there something that could be done to prevent that, and what exactly are the numbers, and so I

would just like to talk briefly about two studies. They're both quite large.

The first was with 36,000 patients who had early-stage breast cancer who had only received radiation for about three months. The question here was how much is that contributing, just radiation alone, and when they looked at all 36,000 patients, only 22 patients had developed MDS or AML, so that's 0.06 percent, so not a large number. But, when they were able to drill down a little bit further, they found that when compared to the general population, those without breast cancer radiation exposure, the risk of developing MDS in these patients was actually 2.3 times higher in the breast cancer patient as compared to normal patients who hadn't been exposed to either. In a second, little bit larger study, because the breast cancer folks and teams and societies are able to enroll lots of patients, and so we're able to learn so much from this information, the clinical trials that they participate in, they looked at 40,000 patients who had stage 0 to 3 breast cancer, so more advanced disease, and these were actually patients who had received surgery, radiation, chemotherapy, or even all three.

Of the 40,000, there were 17 patients with MDS or acute leukemia, 10 with MDS specifically, so again, not a large number, but they did note that their median survival from their MDS was shorter, it was only nine months. So that's consistent with what we had talked about earlier, a few slides back, and they found that the risk of MDS or acute leukemia was about threefold higher than if they had just received radiation alone, and that the risk of MDS and AML was sixfold higher if they received both radiation and chemotherapy. So this is actually something that I talk about with my breast cancer colleagues in the care that they provide to their patients, and they describe to me the conversations that they have and make sure that women are aware of the potential risks, but really it becomes a matter of weighing the risks and the benefits in terms of potentially curing them from their breast cancer and then dealing with these potential complications down the road.

Not to leave the men out, let's talk a little bit about prostate cancer and MDS. Prostate cancer is actually the most common cancer that affects men, and treatment for that includes: radical prostatectomy, so in other words, complete surgical removal of the prostate; something called external beam radiation therapy, which is similar to radiation therapy, for example, that breast cancer patients would receive, where you lie on a table and the radiation is directed at the area of interest; or something called prostate interstitial brachytherapy, and these are the "radiation seeds" that are

implanted within the prostate. For patients with local disease, these are considered definitive therapies or potentially curative therapies, with five-year overall survivals of about 100 percent. But what we think about is that radiation to the prostate does expose the pelvic bones, so your hip bones, of course, is where your pelvis is located, and these actually have more than 50 percent of your total body reserve of the bone marrow.

So, if there's concern about radiation causing secondary MDS, you can understand how there's concern and interest in investigating this further. This has also been looked at in large studies, and while not as large as the breast cancer studies that we just discussed, this particular one looked at close to 11,000 patients with prostate cancer, and of those, 31 patients developed MDS, so that's about less than 0.3 percent. So again, not a large, large number but certainly was present. Sixteen patients had received radiation therapy externally, nine patients had received brachytherapy, or the seeds that are implanted, and the MDS occurred in six patients who had received surgery only. The median time to developing MDS was 8.9 to 13 years, and so this is longer than we would expect with some of the things that we discussed in terms of the topoisomerase II inhibitors or even the alkylating agents.

What this study showed, interestingly enough, was that only patients with advanced age were noted to have an increased risk for MDS, and so it wasn't a clear indication that radiation, at least in this setting in the way that it was given, provided an increased risk for prostate cancer in this group of patients. So that actually is a bit more reassuring to patients, and I think makes people like me, who think about MDS and why it happens, is it something where it's someone who is older who happens to also have prostate cancer who then undergoes radiation therapy, and perhaps it's their age combined with the radiation exposure that somehow increases their risk for having this to happen.

I would like to talk a little bit about lymphoma and myelodysplastic syndromes because, again, it was patients with lymphoma that were also observed to have developed secondary disease. So, just briefly, to talk about what lymphoma actually, lymphoma is a malignant, or cancerous, transformation of lymphocytes, which are a type of white blood cells. Lymphocytes normally travel in the blood and within the lymph node system, and so lymphoma can start and really spread to any part of the body, but typically causes gland or lymph nodes to enlarge, whether that be your lymph nodes in your neck or under your arms, in your groin, or even one of our big lymph nodes inside our

body, our spleen, which actually is a large lymph node. The treatment for lymphoma typically includes chemotherapy, but there can also be radiation and sometimes bone marrow transplantation, usually, typically initially, using your own cells, something called autologous transplant, can be part of the treatment for this disease when it relapses.

For patients with lymphoma, the cumulative incidence, so over many years, of MDS in these patients is about ten percent, and it's very, very clear that patients who have received a lot of chemotherapy are at a higher risk for developing MDS, or even acute leukemia, and so in this particular study they looked at, it's a smaller group of patients, but still provided a lot of information. It was 526 patients who had had lymphoma who underwent bone marrow transplantation, and of those patients, 20 went on to develop MDS or acute leukemia. It was possible for the researchers to identify that there were some very specific risk factors that were more common in those who did versus those who didn't develop disease.

One of them was that they required five days to collect stem cells, so typically when someone is being treated for lymphoma and they need to have a transplant using their own cells, they are hooked up to a machine that's a lot like a dialysis machine that filters the blood and plucks out and removes all of the stem cells. Usually, that can be done in one day or two days, and so the fact that it took five days to be able to collect all of the stem cells that they needed is a sign that there's some damage. It should have been easier to do that, and so there's probably something that's happened to the bone marrow prior to this procedure that's caused it to not work as well as it could have before. They also identified that in the patients who had MDS or even acute leukemia, that they had had prior radiation, particularly something called subtotal radiation, which is a type of radiation that is not really used very commonly now, but many years ago, maybe 20, 25 years ago, was a common way to radiate really all of the lymph nodes in the body with very special radiation techniques and angles of the radiation beams.

So, subsequently, we found that that really increases someone's risk for MDS, and then certainly, as I mentioned, having had a lot of chemotherapy, particularly having four or more prior chemotherapy regimens, particularly with alkylating agents, so the cyclophosphamide, those sorts of drugs that I mentioned on the first few slides back. Their summary or their conclusion was that patients were more likely, or rather it was more likely that there was some sort of mutation that occurred before the transplant even

happened that increased the risk of someone developing MDS, even after a bone marrow transplant had occurred. So I think the concern was that people thought it was just the transplant itself and going through a transplant, but actually no, it's all of the things that really happen and the need for treatment before a transplant even happens that increases someone's risk.

To summarize what we've talked about so far, unfortunately, the overall prognosis for patients with MDS following exposure to chemotherapy or radiation is poor, and the most common type of solid tumor where patients develop this is breast cancer, and it appears as though the risk is higher for those who receive both chemotherapy and radiation therapy. There does not appear to be an overwhelmingly increased risk for MDS in patients with prostate cancer who are treated with radiation. I think the only concern there would really be in your older patients, for example in your 70's and 80's, who have that, could there be some more, or rather a higher risk there. I think that remains to be determined. Patients with lymphoma who received multiple chemotherapies, particularly if they include alkylating agents followed by a stem cell transplant, they are also at increased risk for MDS.

Is there anything new in MDS to help understand more about the role of specific mutations? I sort of have talked vaguely, I think someone might argue, about mutations and that causing MDS. As I mentioned before, until recently, MDS was primarily classified by the way blood cells looked in the presence of specific chromosome abnormalities or changes, and now, actually probably within the past three to five years and with the help of DNA sequencing, the specific mutations that are present within a patient's individual MDS can now be identified. This has been incredibly important and revealing, and I really think it's going to play a role in how we care for patients with MDS, how we diagnose them, and how we ultimately move treatment forward.

The reason for that is because these mutations will help us to understand how it develops, and it will also tell us which mutations are the most important. It will also allow for creation and testing of new targeted therapies against mutations felt to be important. There are a couple of examples of this already, for example there's a mutation called IDH1/IDH2, and there are now very active therapies that are in development, IDH1/2 inhibitors that are being used in patients with AML and other blood disorders, and we think that this is actually going to be effective treatment. More to come on that as we have more experience with those new agents.

So I suppose one of the first questions to ask is really are the mutations in primary MDS, or MDS that comes out of the blue, any different from those in patients who have secondary MDS, and this has actually been looked at, actually recently in one study, with close to almost 500 patients who had either primary or therapy-related AML and MDS. It was a relatively simply idea. They just compared the mutations and how people did, or in other words, their clinical outcomes, based on whether they had primary disease or secondary therapy-related disease. So there were only 28 patients with therapy-related MDS but, even though it was a small group, the information was very revealing. It was able to show that of the 28 patients, there were more patients, first of all, that had intermediate or poor risk disease compared to those who had primary MDS, so based on their IPSS, R-IPSS, there were just more people who had more advanced or high-risk disease compared to primary MDS.

Then, there were 11 patients who actually had mutations, and what was found was that within these patients, there were only two mutations. Ten patients had p53 mutations, and I had mentioned earlier that p53 is very important within your cell, it really tries to shut down anything that's trying to turn into cancer within your cells, and, if that's not there, cancer is more able to happen. Then, there was one patient with an IDH1 mutation, and then, when they looked at patients with primary MDS, they actually found that there were many more mutations present. In fact, there were mutations involving 15 genes, and in contrast to patients with secondary MDS or the therapy-related MDS, very few had p53 mutations, and this suggests that p53 is actually very important in the pathogenesis of therapy-related MDS. Again, just talking a little bit more or further about primary versus secondary, for those patients who had the same R-IPSS score, patients who actually had a therapy or secondary MDS actually did not fare as well and did worse.

So what are the treatment options for patients with secondary MDS that's related to prior chemotherapy or radiation exposure? So the first thing that we have to keep in mind and to think about when we're caring for someone with secondary MDS is that there are more challenges when you're trying to decide on treatment, particularly because patients can have additional medical problems and organ dysfunction that can limit the ability to tolerate chemotherapy. So you have to be aware of the fact that someone could not do as well with treatment you would normally give. Then, finally, someone's bone marrow reserve may not be as great as patients who have had prior chemotherapy. What this means is

that if you're starting off with lower blood counts and you give chemotherapy for MDS, your counts could go lower, meaning you would be at risk for neutropenia and infections, needing more transfusions of blood or platelets, and potentially having an opportunity for more complications because of these low blood counts.

Just as for patients with primary MDS, the only potentially curative therapy is allogeneic stem cell transplantation. Determination of whether this is appropriate or not, in my opinion, should really be assessed as soon as possible once the diagnosis has been made to allow for time for donor identification evaluation, and then also a discussion with the patient's oncologist who is taking care of their primary malignancy to get a sense of whether or not that is active or not, because that can also influence whether or not a bone marrow transplant from another person is possible. Typically, if patients have active other cancers, a bone marrow transplant isn't possible, for the most part, although, again, that's a very individual decision that would have to be made between the patient and their physician. I think it's incredibly important to always consider a clinical trial, particularly given that we know that outcomes for patients with therapy-related MDS are not as good. This suggests that the treatments that we normally give probably could be improved upon.

For the most part, patients are otherwise managed with supportive care or chemotherapies such as azacitidine or decitabine in a similar way to patients who have primary MDS. So what that means is that patients with low-risk MDS in terms of management of their anemia, they could be given growth factor, like Aranesp or Procrit injections, erythropoiet synthetic, erythropoietin. Patients could also just receive supportive care with transfusion of red blood cells and platelets, and this would really apply to patients who for whatever reason wouldn't be able to receive standard chemotherapy. For patients with intermediate or higher risk MDS, depending on the degree of low blood count, something in general that we call pancytopenia, or an increase in the blasts percentage within the bone marrow, we know that the more blasts someone has the more aggressive their disease can become.

So, in those situations, treatment with either azacitidine or decitabine is usually considered. But there can be a consideration for treatment with a standard AML type therapy, something called 7+3, which is a combination of cytarabine and daunorubicin or idarubicin, a much more intensive therapy than azacitidine or decitabine, and actually requires in-patient hospitalization for

about a month or so, and certainly carries more risk, and there could be a potential for more side-effects, as well.

So to summarize, our final summary, MDS that arises after exposure to prior radiation or chemotherapy is called secondary MDS, and this includes MDS that occurs also following the diagnosis of a separate blood disorder, as we mentioned. The incidence, or rather the number of patients who are going to be diagnosed with secondary MDS is likely to increase as more patients are living longer and surviving other cancers. Prior treatment with specific chemotherapy agents leads to very similar chromosomal abnormalities and has a predictable time _____ development of MDS, and we think that this is likely something that's playing a role in the development of the disease.

We also know that, unfortunately, the overall prognosis for patients is poor and that this is due to a need potentially to continue to treat the primary cancer, as well as an inability to maybe tolerate the chemotherapy treatments that are recommended. Treatment with an allogeneic stem cell transplant can be curative in patients with secondary MDS but isn't always an option for a number of reasons. In all other patients, treatment is very similar to what is done for patients with primary MDS, and, finally, considering participation in a clinical trial, if at all possible, is something that I would recommend.

I would like to end here with a picture of the James Cancer Hospital. This is where I spend my time and have the privilege to care for patients with different blood disorders. With that, I would like to end and ask Angie how she would like to proceed in terms of moderating and answering questions if people have them.

Angie Onofre: Thank you so much, Dr. Walker, for your very informative presentation. We did have a few questions come in. Our first question comes from Carlos, and I believe his question is in regards to the new name of the therapy-related myeloid neoplasm. He is asking if that name is new from the current WHO 2016 classifications.

Dr. Alison Walker: Oh, so I'll be honest, I have not reviewed the most recent recommendation, or classification. The therapy-related myeloid neoplasm has been with a previous addition of the WHO, and so I would imagine it was carried forth. I was just on the phone call with the NCCN about the guidelines, and there was no mention of changing the name of that, and so that's not new with this new classification that's just coming out.

Angie Onofre: Okay, thank you. Our next question comes from Lee. She's referring to one of your graph slides, and she was asking if the stats you gave about survival, if that was with or without treatment.

Dr. Alison Walker: Yeah, so that was actually with treatment.

Angie Onofre: Okay. Thank you. Our next question comes from Amy, and she says her family member suffers from, "Shortness of breath and fatigue. His red blood cells are within normal range. What should we discuss with his doctor? He is currently not on any treatment."

Dr. Alison Walker: Yeah, and so I always find that this shortness of breath, fatigue, those are always difficult symptoms. I think it's encouraging that it's not related to the anemia. I've often found, and patients have described to me, and I think it's just their disease, and even though it's not causing the low counts, the disease itself is making them feel fatigued and short of breath. I'm imagining or wondering if it's with exertion or walking around mostly. I think as long as the doctor has ruled out that there's any other causes for those sorts of symptoms, everything else, there's no infection or anything, the heart is okay, as long as all of those things are okay, what I tell people is they have to, unfortunately, figure out how to get through their day in terms of maybe they notice that they have much more energy and they're able to do more in the mornings, or they're better if they're able to stop and take a break and lie down for 30 minutes or an hour and then get up again. Just trying to do their best to make changes and adjust based on how they're feeling.

There isn't anything specific in terms of what I recommend. I don't know of any particular foods or supplements or anything like that. What I do say, I think that when you have MDS, whether you're going through chemotherapy or not, the types of food that we eat I think, just as my doctor tells me, nourishing your body appropriately can only help. So I think trying to stick with the standard things that everybody sort of recommends in terms of diet, and then trying to get some exercise, whether that be just walking. If you're able, I think that that's a help, as well.

Angie Onofre: Thank you. Our next question comes from Allen, and he would like to know if you have any comments on secondary MDS following aplastic anemia, specifically I guess with a treatment regimen of ATG and cyclosporine.

Dr. Alison Walker: Yeah, so that's a great question, and it's very interesting. I had an opportunity to hear Dr. Neal Young talk on this very topic, and it's

sort of the thing that gets our worry up, I should say, when I care for patients with aplastic anemia and whether or not they could evolve to MDS. We find that those patients tend to have more aggressive disease because they tend to develop these chromosome abnormalities in chromosome 7, and really the treatment that is recommended, if possible, is a bone marrow transplant if they can. So I think that that probably would be the first recommendation, and then, otherwise, people are treated with either azacitidine or supportive care, if that's what's indicated, and that, again, this tends to be a much more aggressive disease, unfortunately.

Angie Onofre: Okay, thank you. Our next question comes from Tracy. She would like to know if you can speak on how patients are educated around transfusion-related complications, and who manages these, whether it's the oncologist or general practitioner or hematologist in the U.S. healthcare system. She also has another question asking what is the best form of communication for subjects dealing with all these issues to learn about clinical trial options.

Dr. Alison Walker: In answer to the first question in terms of transfusion-related complications, hopefully I'll be able to answer that. I don't know if that means in the peri-transfusion time period, like during, before, or after you receive the transfusion or sort of long-term. So typically, where I work at Ohio State, we have nurse practitioners who respond to patients who are having any sort of fevers or rash or whatever, or just a fever, changes in their blood pressure during the transfusion administration. They typically handle that, and I would imagine that most oncologists would have something similar in their practice where there's someone on site to help with that.

In terms of iron overload related to transfusions, which is sort of a longer-term issue, that is a little bit more controversial and I think depends on a lot of different very individual factors. In general, patients can certainly receive chelation therapy, which is one way to decrease some of the iron that is absorbed for patients when they need multiple transfusions. Those are the only two things that come to mind with relation to transfusion-related complications. So someone may come to see me in Columbus but receive their treatment two or three hours from here, and so the local oncologist will really handle any sorts of problems that arise. Then, I'm sorry the second question was related to how do people find out additional information?

Angie Onofre: Yeah, she was asking what is the best form of communication for subjects dealing with all these issues to learn about clinical trials.

Dr. Alison Walker: Yeah, so I think that your best option, in my opinion, is actually your oncologist. Even if you see an oncologist who works in a smaller town, they will typically have some sort of relationship or refer patients to a larger center. For example, here at the James, as I said, I work with a number of oncologists who do wonderful and very important work and provide care in smaller communities but will refer patients to me or call me or say, "Gee, is there anything new? I've got a patient with this or that." I think that that's the best way. I personally even have trouble navigating the clinicaltrials.gov website because I feel like even when I look at my own trials, it won't be accurate in terms of what's open or closed. So I really think that that's probably my number one choice, is your own oncologist, and hopefully them reaching out to larger academic centers, like Ohio State or Cleveland Clinic or MD Anderson, that sort of a thing.

I think if that doesn't work for you, thinking about the large academic centers within your state or within your metropolitan area. Many of them, I know here at Ohio State we have what's called the James Line, and so there's a number that you can call that's on our website, and that gets you to a nurse who will get to a doctor and be able to hopefully answer the question. So a little bit depends on where you live and what you have access to, but I guess probably starting with your own doctor is where I would begin.

Angie Onofre: Okay, thank you. Since we're on the topic of clinical trials, are there any clinical trials that are currently active for secondary MDS?

Dr. Alison Walker: Sure. I think many clinical trials are trying to look specifically at this. I would say that there are some clinical trials that exclude patients who have a therapy-related MDS and some that will allow that. I know I had mentioned during the webinar about these new drugs called IDH inhibitors, and I know specifically that patients with secondary MDS or therapy-related MDS were eligible to participate in those trials.

Angie Onofre: Okay, thank you. This question is from Mary, and her sister is currently newly diagnosed. She would like to know what questions should they ask their doctor.

Dr. Alison Walker: So I think probably the biggest questions to ask are whether her diagnosis is considered to be low-risk or high-risk. Low-risk disease tends to be disease that can be managed supportively or not

necessarily with chemotherapy that, for the most part, has the lower likelihood or tendency to transform into acute leukemia. I think if the response is that she has higher-risk disease, then there are a number of questions to ask with respect to that. So number one, is chemotherapy now or later better? We know that when you start chemotherapy for patients with MDS, it's really continued indefinitely as long as it is working, because we know that when you stop the treatment, say someone wants to take a break or they just for whatever reason don't want to do it anymore, if you try to restart it, it's less likely to have the same good benefit in terms of improving the counts and the blasts, or leukemia cell count in the bone marrow going down.

So I think asking whether or not chemotherapy is indicated or not is very important, and then the likelihood of transformation to acute leukemia is also important. I think asking whether or not her sister is a candidate for bone marrow transplant, given that that's really at this point our only potentially curative therapy for MDS. Having said that, patients who have gone through a transplant can relapse after that with their MDS, and so nothing is 100 percent, but I think it's important to find out whether or not it's even an option. Then, finally, of course, asking if there are clinical trials with new therapies, or there's about to be a clinical trial, something called a natural history trial, which is going to be national. It's supported by National Cancer Institute, I believe, or I think it's NHLBI. But basically, we're going to study and learn about patients who have MDS and what happens to them, gain their information, because that's the only thing that's going to be helpful in terms of understanding this disease and coming up with better treatments.

Angie Onofre: Okay, thank you. Our next question comes from Gary. He is asking if there is any connection between shortening telomeres and secondary MDS or relapse after a stem cell transplant.

Dr. Alison Walker: That's a very interesting question. I am very interested in telomeres for a couple of reasons. Probably the first is that there are inherited syndromes that are associated with shortened telomeres and subsequent development of MDS and AML, and so there is probably more at this point a research question as to whether part of chemotherapy, going through a transplant, does that somehow affect telomere length and somehow impact patients. So I don't have a definitive answer to that, or can't give him data or show a graph or anything like that, but if I had to put my money on the table, I would say that there is a relationship between the two. I think telomere diseases, in fact there was just an article in one of

the bigger journals in medicine that was talking about the use of a specific therapy for improvement of telomeres in patients with aplastic anemia and how that improved their blood counts. So I think that there's definitely a role for telomeres and they likely do have some connection. I think it's just going to take more time to further tease that out.

Angie Onofre: Okay, thank you. Our next question comes Leslie. She's asking what is the incidence of MGUS and MDS combined. She says that these two conditions were discovered at about the same time. She is not a 5Q minus but she has responded well to thalidomide and Revlimid therapy, and she was diagnosed 14 years ago and she's been on these therapies for 11 years.

Dr. Alison Walker: Okay. So I think the question is how many patients have an MGUS and an MDS. I don't know that number off the top of my head. I can tell you that MGUSs are common, much more common than MDS, and so I don't know how many patients have both. I'm trying to think in my own clinical practice, which is mostly patients with MDS and acute leukemia and other blood disorders, of my patients with MDS, I would probably say maybe ten percent have an MGUS and an MDS. But I don't know any exact numbers in terms of larger studies that could tell me the answer.

Angie Onofre: Okay, thank you. Our next question comes from Judy and she is asking can a patient just quit responding to treatment, and if so, why would this occur? What factors would be behind this?

Dr. Alison Walker: So people can, unfortunately, stop responding to therapy, and it could be for a couple of reasons. It could be that the MDS has acquired new and different mutations, and so even though you had a therapy that was very effective against the first group of mutations that were there, the MDS somehow is able to outsmart that and new mutations arise to try to get around that new therapy. So that's probably what happens and why we see relapse occurring. Typically, it requires some change in therapy, if possible, if that does occur.

Angie Onofre: Okay, thank you. We have time for just a few more questions. This other question is from Gary. He is asking is it possible to start Vidaza after stopping previously with good results?

Dr. Alison Walker: Is it possible to stop – I'm sorry. Could you say that again?

Angie Onofre: Is it possible to start Vidaza again after stopping previously with good results?

Dr. Alison Walker: So it's something that people can do. My personal experience and how I practice is I mention to people that sometimes it doesn't work as well, or work at all if you stop and then restart, and so for my patients, I don't recommend interrupting therapy, if at all possible.

Angie Onofre: Okay, thank you. I believe we have time for one more question. This question comes from Patricia. She says her blood counts are in low-to-normal range but her white blood cells are extremely low, and she would like to know why there is such a big difference. She just had a bone marrow biopsy and her marker is at 71 percent.

Dr. Alison Walker: Okay. So I absolutely do see patients like this who have, for whatever reason, one of their blood counts may be more affected than another. So with respect to the white blood cell count, that typically of course would only be a problem if it gets to a point where someone is having repeated infections, and so sometimes that's just how people look and are different with respect to their MDS and how it affects the three different cell lines. So it is something that's common and it's not unusual to not have everything affected equally.

Angie Onofre: Okay, thank you. Thank you so much once again, Dr. Walker, for your wonderful presentation and for your time. Just as a reminder, everyone that is on the webinar or has previously registered for the webinar will get a notification letting them know that the webinar will be archived, which will happen within five to seven business days. On behalf of the Aplastic Anemia and MDS International Foundation, I would like to thank each and every one of you for joining us today and making us your resource of choice for information on bone marrow failure diseases. If we were not able to answer your question today, please send it to us via e-mail at help, that's help@aamds.org so that our patient educator can respond, or visit our online academy at aamds.org/learn for interviews with experts and other programs that may address your questions. As a reminder, as soon as I'm done speaking, a post-event survey will appear requesting your feedback. We appreciate your time to complete this survey. Again, thank you for joining us, and remember, learning is hope. This concludes today's program.

[End of Audio]