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INTERNATIONAL FOUNDATION

MDS Update

Connecting Patients and Families with News and Expert Opinion

INTERVIEWS WITH THE EXPERTS

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Genetic Mutations in MDS

Q What are genetic mutations and why are they so important for MDS patients to know about?

A Myelodysplastic syndromes are a group of very different diseases. These diseases are grouped under one name, but there are many different types of MDS and each can have a very different outcome. For years we have been able to identify the different clinical features of each MDS type, and we have also known what clinical features seem to be prognostic (i.e. help us understand how the patient will progress over time). We now also know what genetic mutations (DNA change) are prognostic.

A DNA mutation is an abnormality in your DNA that you acquired – it was not present at birth. This mutation impacts survival, and MDS itself. We have learned which of these mutations are the most significant. If you have MDS with several mutations, your prognosis may be worse and therefore, you may need a more aggressive treatment.

We know that there are some mutations which are correlated with a very good prognosis, including one mutation known as SF3B1. The patients who carry this mutation tend to have a better outcome. They need to be treated, but less aggressively.

We also know that with certain mutations like B53, the outcome may be very poor and so patients need to pay close attention to the treatment they are going to receive. This is relatively recent knowledge and needs more study. But for many other mutations we know a lot about—we can treat these in a prescribed way.

Q Why do DNA mutations occur that make it more likely to get MDS?

A As we get older, we have more abnormalities in our DNA. That doesn't mean that everybody has them-- but a proportion of people over 70 will have some abnormality in their DNA. This doesn't mean that you will have or will get MDS. But it has been shown in several studies in the last few years that mutations that are very tiny may expand their clone to other cells that will then also carry the mutation. These changes can allow for development of hematological malignancies like MDS.

Dr. Valeria Santini

Dr. Valeria Santini is an Associate Professor of Hematology at the University of Florence in Italy. This interview was recorded at the American Society of Hematology Annual Meeting in December 2017.

So even though MDS is not in evidence, there is clonal hematopoiesis—a group of cells carrying a specific mutation although there is no evidence of disease. But about 1 percent may develop MDS or some other malignancy over the years.

Q What is the association between genetic mutations and personalized medicine?

A The presence of inherited DNA mutations that get passed down from parent to child are extremely important in determining or changing treatment. Our approach now must be to look at all these variables—the clinical, individual, and molecular variables, to determine the best possible treatment. There are already some drugs that target some specific mutations. We think that in the future we will be able to select patients based on their grouping of DNA mutations and approach this with new targeted drugs. We want to eliminate the abnormal clone, and eliminate the cells it affects.

Q What else do you think is important for patients to know to be informed and involved with their treatment?

A They should know that there are experimental drugs that are extremely promising in targeting the specific mutations. They should also know that physicians are generally aware of the established individual and molecular variables, and hematology is addressing these problems accordingly. Patients should know that there are many ways to be treated—different treatment and therapies using different agents. Doctors are trying to use the best treatment pathway for every patient.

2018 Scientific Symposium Patient Summaries and Videos

Our recent AAMDSIF 2018 International Bone Marrow Failure Disease Scientific Symposium brought together a group of international leaders in research and treatment to discuss current knowledge and promising future therapies. Our *Summary for Patients* booklet includes lay language summaries of all symposium presentations. Here, we present one of the several presentations on the biology and treatment of MDS and secondary AML.

Download a copy at https://bit.ly/2KeEpE4, email us for a print version (orders@aamds.org), or call 301-279-7202 x 116.

Also, be sure to view our interviews recorded at the symposium, (www.youtube.com/AAMDSIF).

New Therapies for Anemia in Low-Risk MDS

Aristotles Giagounidis, MD
Marien Hospital Düsseldorf

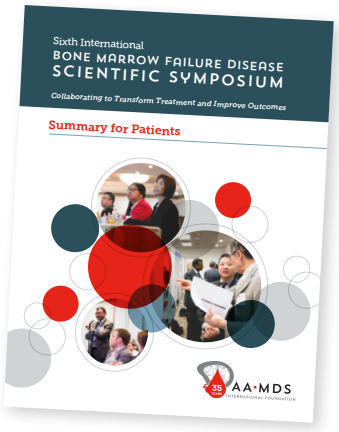
Patients with anemia have low levels of red blood cells or hemoglobin, a protein in red blood cells that transports oxygen. Anemia is common in MDS because the bone marrow doesn't make enough healthy red blood cells. It can cause fatigue and low levels of energy.

The most common treatment for anemia in low-risk MDS consists of erythropoietin-stimulating agents (ESAs). These drugs can delay the need for red blood cell transfusions. But if a patient doesn't respond to ESAs or if the ESAs stop working, treating anemia can be challenging.

Some ESAs for anemia in low-risk MDS are being studied. For example, an international Phase III clinical trial compared the efficacy and safety of epoetin alfa (Procrit or Epogen), an ESA, to placebo in 130 patients (median age 75) with low-risk or intermediate-1-risk MDS. Red blood cell counts returned to normal in 32% of the epoetin alfa group and 4% of the placebo group. The proportion of patients needing red blood cell transfusions dropped from 52% before the study to 25% by week 24 in the epoetin alfa group. Epoetin alfa was as safe as placebo.

A patient is most likely to respond to epoetin alfa if his or her blood level of erythropoietin, a hormone that helps the bone marrow form red blood cells, is below 200 units per liter, and the patient has had no red blood cell units transplanted.

Another Phase III clinical trial evaluated darbepoetin alfa (Aranesp), an ESA, for 24 weeks in 147 patients with low-risk or intermediate-1-risk MDS.



Darbepoetin alfa reduced the number of transfusions that patients needed significantly compared with placebo. Eleven patients (14.7%) treated with darbepoetin and none treated with placebo had an erythroid response, meaning that their red blood cell counts returned to normal.

This response rate might seem surprisingly low. But it is due to the complicated study protocol that required doctors to interrupt treatment at certain points. In the real world, darbepoetin response rates are at least as high as, if not higher than, those of other ESAs.

Instead of an ESA, a third Phase III study assessed the effects of lenalidomide (Revlimid) in 205 patients with lower-risk del(5q) MDS who needed regular red blood cell transfusions to treat their anemia. Significantly more patients stopped needing transfusions for at least 26 weeks with either 10 mg or 5 mg lenalidomide than with placebo. In another study, 27 patients with lower-risk del(5q) who needed regular transfusions halted lenalidomide treatment when they stopped needing the transfusions, which was safe and didn't lead to disease progression. Lenalidomide seems to work best in patients who have del(5q) MDS and erythropoietin levels of 100 units per liter or less. However, patients who have MDS but not del(5q) don't respond to lenalidomide for long—less than a year on average.

Luspatercept is an investigational drug that increases red blood cell levels in patients who have anemia due to MDS. A Phase II clinical trial assessed various doses of this drug in 73 patients (median age of 72 years) with lower-risk MDS. Sixteen of 22 patients (73%) who had needed fewer units of transfused red blood cells before the study and were treated for more than 3 months had increased red blood cell counts and hemoglobin levels, as did 16 of 20 (80%) of those who had needed more units of transfused red blood cells. Furthermore, 17 of 28 patients (61%) who had needed red blood cell transfusions before the study stopped needing them for at least 8 weeks after 3 months of luspatercept treatment. Response rates were highest in patients with erythropoietin levels of 500 units per liter or less and those who had an SF3B1 mutation. Most side effects were mild.

MEDALIST is an ongoing Phase III study of luspatercept in patients with very low-risk, low-risk, or intermediate-risk MDS with ring sideroblasts who need red blood cell transfusions. The patients have not responded or stopped responding to previous ESA treatments or their erythropoietin levels are higher than 200 units per liter.

PATIENT STORY

Patient Trusts Her Instincts in Finding the Right Treatment

Sherry Pratt

I never thought I would be diagnosed with cancer. I taught exercise classes, walked every day, ate a Mediterranean diet, and paid attention to products I used on my skin. I became a certified health coach and taught healthy living classes.

But I did get a cancer diagnosis —a rare blood cancer called MDS (myelodysplastic syndrome). Specifically, it was the Refractory Anemia with Ringed Sideroblasts, (RARS) subtype. I was scared, mad, confused, and in denial.

When I was first diagnosed in August 2014, my hemoglobin was in the 9's. (normal is 12-18) and I had no symptoms. I just thought I was getting tired on some days because I was getting older.

After my second bone marrow biopsy, I my local oncologist stated that I would get eight weeks of epoetin alfa (Procrit®) injections and that if my counts didn't improve, he would give me chemotherapy but wasn't any more specific than that. He could not tell me the specific type of MDS I had so I decided to go for a second opinion.

A friend of mine suggested the Ochsner Clinic in New Orleans. The oncologist there did my third bone marrow biopsy, and determined I had the RARS subtype of MDS. He started Procrit® along with vitamin B12 and B6. Months later I began lenalidomide (Revlimid®) but after six months, no improvement was seen and my hemoglobin counts continued to slowly decline. My local doctor and my doctor at Ochsner agreed that the next step should be azacitidine (Vidaza®). I was scheduled to begin the azacytidine by infusion in August 2016 and continued to be treated locally with Procrit®.

A friend of mine, Susan, asked if I had ever considered the Cancer Treatment Centers of America. After much prayer and a nudge from God, I decided to go there for a third opinion. My siblings all encouraged me to go there. So, in August 2016 I sent a letter to my local doctor and the Ochsner doctor telling them of my decision to go to CTCA for a third opinion and to put my current treatment plan on hold.

In September, my husband Wally and I visited CTCA for the first time. When we entered the foyer of the hospital, there was a lady on the second floor of the foyer playing "Amazing Grace" on a grand piano. I had read my devotion that morning and it said," Today, you are marked for a miracle."

When I first got to CTCA, I started on decitabine (Dacogen®) using a five day/1-hour infusion. It dropped my white blood cells very low, my red cell count to 6.7 and my platelets to 11. I had to get blood and platelet transfusions. It took 40 days for my ANC to get to normal.

Then I took another round of Dacogen® but for only 3 days, with the same results. Neither round helped to increase my red blood cells, and it took 40 days for my ANC to get back to normal. Finally, my doctors at CTCA decided to prepare me for a stem cell transplant.

I met with the head of the stem cell unit and he said he wanted to test my sister Sonya (who is just 6 years younger than me) to see if she might be a match. He warned me that the possibility of her being fully matched was only 25%. She took her blood test in October of 2016.

On November 3, 2016 we received the good news that Sonya was a 100% match. She arrived for her stem cell harvest preparation in December 2016. She would be given a series of two injections per day to increase the number of stem cells in her body. My pre-transplant conditioning chemotherapy began in December.

For Sonya's collection process, members of the treatment team inserted a peripheral line in both arms. They drew blood from the left arm through an apheresis machine which spun off her stem cells into a bag and then pushed her blood back into her body via the line in her right arm.

January 3, 2017 was transplant day. I received 7.6 million stem cells from my sister Sonya. The next 24 days were a little rough at times. I was weak but had to get up and walk every day and use an exercise bike in my room. Sometimes I had as many as 12 IV bags on my pole. During the 30 days in the hospital I had some fevers a few times, and several transfusions. After transplant, your blood count numbers drop but when engraftment begins, they slowly rise.

I read Bible verses every day and said the Lord's Prayer to get through any discomfort. I was able leave the hospital room and return to my own quarters in the hospital on Jan 24th, 2017. I remained there for the rest of my 100-day stay at CTCA.

I returned home to Mississippi in April 2017. I had to get my blood tested weekly for a while. At first, I went back to CTCA as frequently as every week, then every month. Soon it was 2 months and now it is every 3 months. My last visit to CTCA was Jul 2, 2017 and my doc it's said I am doing fabulous! I am no longer on any medications!

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AAMDSIF - Your best resource for medical and personal perspectives on myelodysplastic syndromes (MDS)

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- Your Guide to Understanding Clinical Trials **
- Your Guide to Understanding Bone Marrow and Stem Cell Transplantation **

*Available in French, German, Italian, Portuguese, and Spanish
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Living with Aplastic Anemia, MDS and PNH
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