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Updates on Sickle Cell Disease From ASH: A Hematologist's Perspective

Dr. Turck:
A large number of patients with sickle cell disease experience extensive morbidity and even early mortality, but in recent years significant progress has been made in the treatment of this disease, which has led to increased survival rates. What do we need to know about this progress?

Welcome to *ASH Action Center* on ReachMD. I'm Dr. Charles Turck. And joining me today to share insights from the 64th ASH Annual Meeting and Exposition is Dr. Clifford Takemoto, the Chief of the Clinical Division of Hematology at St. Jude Children's Research Hospital in Memphis, Tennessee.

Dr. Takemoto, thanks for speaking with me today.

Dr. Takemoto:
Thanks for the invitation.

Dr. Turck:
Let's start off with some background. Dr. Takemoto, how do we currently manage patients with sickle cell disease?

Dr. Takemoto:
Yes. So I, I would start out by saying that sickle cell disease is, is the most common genetic hemoglobin disorder that hematologists see, and it's a chronic condition that affects about 100,000 people in the United States, most commonly people of African ancestry but also people of Middle-Eastern and Indian ancestry. The reason for this is because of its protective effect against malaria. What we know about this condition is that it, it also affects populations with great, healthcare disparities, and this is not only true in the United States but globally.

I think about the care of patients with sickle cell disease in three different categories. One is health maintenance, and these are patients that we see on a very regular basis, and we partner with primary care physicians to deliver that care. I'm in pediatrics, and I would say that the majority of patients in the pediatric age range are seen by pediatric hematology providers with expertise in this area. It's a challenge when patients move to the adult care, and that's just because there are fewer providers that have expertise in this condition, so access to care and education about appropriate management is, is the care gap I would say.

The second area that people need to be knowledgeable about is how to manage acute complications. Pain is a very common symptom that we see, and knowledge about how to manage that is very important. Infection, acute chest, chest syndrome, which is inflammation of the chest, and stroke are also common complications.

And lastly, I would say that chronic complications are another very large problem that we see not so much in the pediatric population, but what we're learning about sickle cell is that these are complications that really affect the adults, and one of the challenges is, is to know about interventions that we can implement to decrease these complications long-term.

Dr. Turck:
And are there any emerging therapeutic developments that we should be aware of?

Dr. Takemoto:
So at this most recent ASH meeting, there were three different areas that I thought were very informative and provided education. One, is actually just the implementation of applying or implementing standard care that we know is important. This is really implementation of,

of what we know is, is the best therapy, things like, penicillin prophylaxis in children, transcranial doppler screening, to prevent, or to screen for stroke risk, and also to provide access to care. These are, implementations of, of standard care guidelines that are not always standard at different institutions. In particular, I think this is a challenge in the adult population where there are fewer providers and fewer hematologists, to provide care for patients with sickle cell disease.

In terms of new therapeutic developments, this has been an area that I, I found very exciting. Many years, since the late '90s, we've only had hydroxyurea as, what I call disease-modifying therapy, meaning that it's not treatment for pain or for any of the acute complications, but it's really preventative. And, since that time there's been a real paucity of, progress and new therapies, but over the past five years, there's been three other, therapeutic options now available for patients. One is L-glutamine, uh, which has been shown to decrease pain episodes in, in patients with sickle cell disease. Uh, the other is voxelotor, which is an antisickling agent, uh, and, and, and the fourth is crizanlizumab, which is a P-selectin inhibitor, which seems to decrease the risk of pain, so those disease-modifying therapies are relatively new. We're still learning how to use them, but these are, these are therapies that all hematologists should be familiar with.

There are other therapies that are on the horizon. There are several in trials now. Many of them were talked about at the meeting. I'll just highlight one of them. One is a, is a pyruvate kinase agonist. So there are people that have pyruvate kinase deficiency, which results in anemia, but what we also are learning is that medications that actually activate pyruvate kinase can improve hemoglobinopathies, and that seems to be in part because of decreasing sickling, shifting the oxygen saturation curve.
So these are, these are new disease-modifying therapies that are on the horizon.

The last big category of therapeutic developments which there's a lot of excitement about are what I would call in air quotes, curative therapies, and this would include, bone marrow transplantation, which has been a curative therapy, that has been around for several years now, but also gene therapy. So there, there are now, several trials that have applied gene therapy technology to treat patients with sickle cell disease, and so there were a number of, of talks about targets for gene therapy.

Dr. Turck:
For those just tuning in, you're listening to *ASH Action Center* on ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Clifford Takemoto about insights into sickle cell disease from the 64th ASH Annual Meeting and Exposition.

Now let's focus on some of the clinical research presented at the conference. Dr. Takemoto, if we focus on one patient population in particular, what did we learn about managing sickle cell disease in pediatric patients?

Dr. Takemoto:
So, as a pediatric hematologist, I would say that what we've learned is that many of the therapies that we now can prescribe to patients are quite effective in decreasing acute complications and chronic complications. One of the areas that we are understanding though is that the complications that patients are subject to can arise later on in adulthood, so that is I think one of the areas as pediatricians we need to know and think about how we can keep people healthy for their lifespan. It's a condition where the lifespan of a patient with sickle cell disease is shorter, and in the '90s, there had been studies showing that the average lifespan is in the 40s. That has thankfully been shown to be longer these days with these new therapies, but I think as, as, as pediatricians with all these new therapies, this is the next question, is how can we use these to prevent chronic organ disease and damage in the adult patients.

Dr. Turck:
And what about pregnant patients? What are some of the latest clinical developments in care for that patient population?

Dr. Takemoto:
This is an area that has not, I think, received a lot of attention. At the, at the ASH meeting, there were two education sessions that highlighted some of these issues that we see with patients with sickle cell disease. One was the question about fertility. And what we've learned about fertility in women with sickle cell disease is that there appears to be a reduction in what they call the reproductive lifespan of women with sickle cell disease, meaning there's a shorter window of fertility, and this appears to be due to reduced ovarian reserves, and the thought is that it may be a combination of disease itself, but also, there's a lot of questions about some of these new disease-modifying therapies, like hydroxyurea, what, what impact it has on fertility. In addition with other therapies like bone marrow transplantation and gene therapy, there's a lot of questions that are, are now coming up about fertility with these treatments.

The, the second area that was highlighted at, at the meeting was the, the realization and the understanding that there is a substantial increase in morbidity in, in women who undergo pregnancy. In populations and in low- and middle-income countries, the risk and incidence of death with pregnancy is many-fold higher than in the United States and Europe. This appears to be secondary to most commonly from acute chest syndrome and pulmonary embolism, and this really highlights the need for multidisciplinary care in patients who are pregnant.

Dr. Turck:
Switching gears here a bit, would you share some the latest clinical updates concerning mortality in sickle cell disease?

Dr. Takemoto:
As, I mentioned, it appears that the lifespan of individuals with sickle cell disease appears to be lengthening and, and longer than what was, described several decades ago, but there's a long way to go, and we are still—we see organ damage in patients who are adults, and so that is, again, that is one of the challenges that we have to try to increase and, and improve the care of patients with sickle cell disease.

There are, several ways to approach this. One is to look at the effect of healthcare disparities and, and, and how can you address and improve access to care. So these are really just implementation of things that you know are, are the best way to treat patients, and the hope is that this is—this results in better outcomes and, and improved survival in patients with sickle cell disease.

The question about how new therapies, including disease-modifying therapies that I had talked about but also curative therapies, how that's going to impact mortality is really—there's a lot of enthusiasm and hope, but there's a lot of questions. In some ways there's a lot of unknowns about that, but there's enthusiasm that this may be an approach that, that will be available to many patients in the near future as we, determine the safety and efficacy of these therapies.

Dr. Turck:
And before we close, Dr. Takemoto, do you have any lessons or takeaways from the ASH Annual Meeting that you'd like to share with us?

Dr. Takemoto:
I would say that one of the, the big takeaways is just the importance of education. As I think about the meeting and some of the highlights and how—in terms of how we can improve care, one is, again, is educating providers to know how to deliver the best care, because we have many studies that show therapies that are, that are, beneficial to patients, but they're not getting out to all patients, so I think that's one, and that's one, um, one of the values of conferences like ASH.

The second big area, because there's so much enthusiasm about new therapies like, like gene therapy, is to also think about the safety. And we are also learning about the risks of toxicities like the risk of leukemia and cancers, and in other sessions of, of—in the, in the meeting, there were, there were talks about genetic changes and small clones that are sentinels of the development of leukemia, so some of the things that we learn in other diseases I think will be very helpful to understand risks and safety for some of these novel therapies like gene therapy and bone marrow transplant in our patients with sickle cell disease.

Dr. Turck:
Well, with those interesting thoughts in mind, I'd like to thank my guest, Dr. Clifford Takemoto, for joining me to share his insights on sickle cell disease.

Dr. Takemoto, it was great speaking with you today.

Dr. Takemoto:
Thank you, Dr. Turck. It was a pleasure.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this episode and others from our series, visit ReachMD.com/ASHActionCenter where you can be Part of the Knowledge. Thanks for listening.