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The Current Standard of Care and Unmet Need in Anemia of CKD

Announcer:

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Here's Dr. Sophia Ambruso.

Dr. Ambruso:

Hi I'm Dr. Sophia Ambruso. I'm an assistant professor on faculty at the University of Colorado, and today we're here to talk about current standard of care and unmet need in anemia of chronic kidney disease.

These are my disclosures.

So let's get started with discussing KDIGO recommendations for anemia of chronic kidney disease. Iron deficiency plays a crucial role in the anemia of chronic kidney disease. [KDIGO] As such, iron supplementation is an important component of the standard of care of these patients. Once diagnosed, a trial of IV iron, at least in dialysis dependent patients, is recommended for those who have iron deficiency anemia. [KDIGO]

Erythropoiesis stimulating agents, ESAs, are a second step in therapy and often used in combination with iron supplementation. [KDIGO] One thing we have to remember is that iron is an essential building block for our red blood cells. So we select iron first because ESAs will not work if we don't have those building blocks to make our red blood cells. [Localetti] We will utilize ESAs when hemoglobin concentrations drop below 10 grams per deciliter. [KDIGO] Blood transfusions are a rescue therapy if other treatments for anemia fail. [KDIGO]

So before we go further, I want to take us through the history of anemia management and chronic kidney disease. It's hard to believe that prior to 1986, we were reliant upon blood transfusions to treat anemia of chronic kidney disease, and this was fraught with many complications mainly related to iron overload and blood transfusion reactions. [Eschbach]

After the discovery of ESAs in 1986, things changed and the landscape of anemia management was transformed. [Eschbach] In the late 1980s/early 1990s, ESAs demonstrated improved quality of life [Evans] and reduced blood transfusions [Eschbach], but not too long afterwards, we discovered that there was increased cardiovascular risk and myocardial infarction associated with ESAs. [Besarab; Singh, 2006; Drüeke] In fact, the Normal Hematocrit Study was terminated early for these reasons. [Besarab] In the mid 2000s, CHOIR and CREATE trials were released. [Singh, 2006; Drüeke] The CHOIR trial demonstrated that increased hemoglobin was associated with increased risk of cardiovascular disease, [Singh, 2006] and the CREATE trial demonstrated that there was no reduced cardiovascular risk with early anemia correction. [Drüeke]

In the mid 2000s, the TREAT trial was released, which targeted a goal of approximately 13 grams per deciliter of hemoglobin, and that was associated with an increased incidence of stroke. [Pfeffer] This cumulation of data resulted in the ESA boxed warnings. It recommended hemoglobin levels within 10 to 12 grams per deciliter, which was revised in 2011. [FDA Safety Communication] And then a year later, KDIGO released their guidelines on the management of anemia of chronic kidney disease with iron, ESAs, and red blood cell transfusions. [KDIGO]

Then in the mid 20 teens, the PIVOTAL trial was released, which demonstrated that high dose proactive iron was superior to low dose reactive iron. [Maddougall] And that's essentially where we are currently today with the use of iron followed by ESAs, and transfusions as rescue therapy.

So let's talk about ESAs a little bit more. We have patients who are considered to be ESA hypo-responders and they require higher doses to increase and/or maintain their hemoglobin levels within the acceptable range. [Khankin] In fact, up to 13% of patients with anemia of CKD are considered hypo-responsive. [Luo] ESA use is two to three-fold higher in those who are hypo-responsive; [Luo] and they also have poor clinical outcomes and they have increased risk of cardiovascular disease and all-cause mortality. [Ogawa]

[Slide 7]

In fact, these patients have a five- to seven-fold higher transfusion burden than those who are ESA responsive. [Sibbel] So let me get you oriented to this slide. Over here on the left, this is going to be looking at percentage of patients of hemodialysis who received transfusions. The Y-axis is percent of patients. The X-axis is the month. Up top, we have our chronic hypo-responders. This is the square. And what we see is that they have a seven-fold higher monthly burden of transfusions. The orange triangles are acute hypo-responders, and early on we see a five-fold risk of transfusion burden. We do see that that risk gap changes over time, and then it decreases to about a two-fold greater burden compared to the ESA responsive group. [Sibbel]

So let's talk about transfusions and why we want to avoid them in our dialysis patients. But first we need to understand that approximately 23% of patients on dialysis have received at least one blood transfusion. [USRDS]

So why does this matter and why do we want to avoid transfusions? Transfusion can result in clinically significant increases in antibody production because there is a foreign entity from another person's body. The blood product that's put in the body makes antibodies against this, and that can cause allosensitization. This results in the increased risk of transplant rejection and poor graft survival. Patients have longer wait times or may never receive a transplant because of this. [Loupy] Highly sensitized patients require complex and costly treatments, and this is why KDIGO recommends we avoid transfusions, if possible. [KDIGO]

So let's talk about disease management considerations with our current interventions and our standard of care. Oftentimes we need to take into consideration the administration route, [Bonomini] whether or not a patient needs to travel to clinics, or whether or not the medicine needs cold storage. [Bonomini] For example, if patient needs IV iron, then they may need to go to an infusion clinic or they may need to go to their dialysis unit. Additionally, ESAs require cold storage. [Bonomini] Also, there are specific considerations based on the treatment options as well as shown here. For iron, it may minimize blood transfusions or anemia related symptoms. [Bonomini] We know that it can enhance erythropoiesis and raise hemoglobin levels by providing the building blocks. [KDIGO]

But the cons include that oral iron is fraught with GI side effects [Roger], including constipation, which occurs often, and many patients end up not taking their medication. [Roger] IV iron can result in anaphylaxis. [Roger] There's also iron toxicity, and then there's an increased risk of infection. [Roger] From an ESA perspective, it may minimize blood transfusions and anemia related symptoms, but there's increased cardiovascular risk, and some people are ESA hypo-responsive. [Bonomini] And then of course, we know from a blood transfusion perspective, it may be necessary, but it does have a lot of risks associated with it, which we've already discussed. [Loupy; KDIGO]

So what gaps remain in the management of anemia of CKD? I think we've touched a bit on the patient and healthcare provider issues, but more importantly, we need to become more active in our shared decision making with our patients and be more sensitive to patient preferences, which include the route and frequency of administration and the effectiveness of the hemoglobin control based on our current options. [Bonomini; Frazier] So the role that we can play in improving this is beyond our clinical parameters. We can assess comorbidities and monitoring for anemia symptoms and complications. We can weigh risks and benefits when deciding which initial therapy we'd like to select. We need to be really careful in terms of how we are prepping patients for dialysis and use shared decision making. And we also need to use patient reported outcomes to improve our patient care. [Rosenberg]

We also need to assess patient reported outcomes to provide care that better suits our patient needs. [Locaetti] So in summary, our current standard of care for the treatment of anemia of chronic kidney disease includes iron, ESAs, and blood transfusions. [KDIGO] The challenges in disease management remain, and that includes ESA hypo-responsiveness, blood transfusion burden, and implications on transplant outcome, in addition to the socioeconomic, racial and geographic disparities. [Bonomini; Roger; Loupy; KDIGO; Rodriguez] A patient-centered approach to treating anemia of chronic kidney disease is vital and it should include greater patient and healthcare provider education, which will lead to shared decision making. [Mathias]

Thank you for listening, and I hope you found this presentation helpful for practice in the management of anemia of CKD.

Announcer:

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