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Beyond Steroids in Warm AIHA: A Practical Framework for Diagnosis, Relapse Management, and Emerging Therapies

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Dr. Piatek:
Welcome, this is CE with GLC. I'm Dr. Caroline Piatek.

Dr. Nguyen:
Hi there. I'm Dr. Anthony Nguyen.

Dr. Piatek:
Today, we'll be diving into some of the biggest challenges in the management of warm autoimmune hemolytic anemia, or wAIHA, in signature clinical countdown style: fast-paced, practical, and focused.

Dr. Nguyen:
Throughout this program, we'll cover a practical approach to diagnosis, review the current treatment landscape, and discuss emerging therapies that may help shape future management for patients with wAIHA.

Dr. Piatek:
Okay, so let's get started. So, Anthony, what's your approach to the evaluation of a patient with suspected wAIHA?

Dr. Nguyen:
So in terms of approaching it, usually we get referrals from our primary care physicians or hospice.

So, typically, the patient has severe anemia. When I say severe anemia, the hemoglobin is <7. There are positive hemolytic markers, undetectable haptoglobin, positive direct antigen testing, and also elevated unconjugated bilirubin, elevated reticulocyte count, and also, again, severe anemia, typically a hemoglobin <7.

And those are typically the signs that we'll see. The physical exam findings usually include a patient who's fatigued, short of breath, also is jaundiced and has scleral icterus.

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Dr. Piatek:
So, yeah, just kind of building on what you've said, I think the interpretation of the hemolytic markers can sometimes take a little bit of effort. So the LDH can be elevated for or is a nonspecific marker of cellular turnover. The haptoglobin may be low in the setting of liver disease, for example.

And then, also, it's important to note, although we think of reticulocytosis as being characteristic of hemolytic anemias, about 20% of these patients with wAIHA will actually have reticulocytopenia, so that's just something to be aware of as well. I mean, as you mentioned, the Coombs test or the direct antiglobulin test is going to be our most important test for the diagnosis of warm autoimmune hemolytic anemia.

So we're expecting that to be IgG ± C3 positive. There are a subset of patients, maybe 5% to 10% of patients, who will be DAT-negative. So there are reference labs that you can send out to evaluate for IgA, IgM subtypes, or low-affinity antibodies, so that's just something to keep in mind.

And then, it's of also the peripheral blood smear can be helpful in the evaluation of warm autoimmune hemolytic anemia. So you can see polychromasia, which is a marker of the reticulocytosis, and then also see the spherocytes for these patients.

Dr. Nguyen:
Some of the time we do get Coombs-negative warm autoimmune hemolytic anemia, and in those cases, sometimes I do send lab specifically to a reference lab called Versiti to evaluate Coombs-negative warm autoimmune hemolytic anemia.

But the challenge, the diagnosis, I think, should be, once it's suspected, the diagnosis is definitely important to make while the patient is in the hospital and also outside the hospital for very fast treatment and quick treatment because of the severity of anemia.

Caroline, once you've confirmed the diagnosis, do you risk stratify patients with wAIHA?

Dr. Piatek:
So there's a couple of ways to risk stratify these patients. So the most important marker for disease severity is going to be the anemia or the degree of anemia on presentation.

So the more severe the anemia present, the more difficult to treat the disease is, and the higher the risk of mortality. We also know that reticulocytopenia, or a low or inappropriately normal reticulocyte count, is also a predictor of poorer outcome as well. And this represents the fact that the bone marrow is not able to compensate for the degree of hemolysis that's present.

And so here, the antibody that's attacking the mature red blood cells is also attacking the immature red blood cells in the bone marrow as well. Additionally, the DAT subtype or pattern is also a marker of a more difficult-to-treat disease. So when you have patients who have mixed AIHA or atypical AIHA or Evans syndrome, these are all patients that are more challenging to manage.

I'll also add that the degree of hemolysis is also associated with the risk of venous thromboembolic events as well, which is another well-known complication of this disease.

Additionally, it's important to consider whether this is primary or secondary wAIHA. And so, based on your evaluation of the patient, you may also be looking at or looking for an underlying autoimmune disease such as lupus, as well as a lymphoproliferative disorder such as lymphoma, depending on the patient's presentation.

Dr. Nguyen:
Thanks, Caroline. No, I totally agree. Also, what I take into account, especially when the patients are in the hospital, the need for transfusions. Sometimes patients need transfusions immediately. In that case, all blood will be incompatible due to the degree, due to the high levels of warm autoimmune antibodies.

But we always ask the blood bank to transfuse the least incompatible blood that's possible. So the need for transfusions also helps me gauge the need and also frequency of transfusions also helps me gauge the disease severity too.

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Dr. Piatek:
Right. And so I think it's important to not withhold transfusions in these patients. So typically, this threshold's going be around <6 for transfusion in this patient population.

Dr. Nguyen:
Oh, one cause of autoimmune anemia or warm autoimmune hemolytic anemia that we've seen is with immune checkpoint inhibitors. So that's another cause of or secondary cause of medications is one that also should be considered too.

Dr. Piatek:
Let's move on to treatment sequencing. Anthony, how do you monitor treatment response? And when do you decide to move on to therapies beyond steroids?

Dr. Nguyen:
Yeah. So typically, Caroline, as you mentioned, steroids are our mainstay of treatment for wAIHA for many, many years since previously there was no FDA-approved treatment for wAIHA.

And typically, we will start steroids at 1 to 2 mg/kg daily for patients. And typically, I will start steroids every single day while the patient's in the hospital or as an outpatient and also start making sure I start prophylaxis. I'll start a PPI in addition to the steroids.

But typically, we'll keep the patient on a high dose of steroids for at least 2 to 4 weeks to see if we will see a response in anemia, meaning the hemoglobin improves, LDH improves, haptoglobin (it becomes detectable), and also unconjugated bilirubin decreases. And typically, that will take anywhere from 2 to 4 weeks.

What I see typically is that for patients who are referred to me is that the patients have not had an adequate or long enough duration or high enough dose of steroids typically when they are referred. At that time, then that's when they're referred to us for a second opinion.

But typically, I give patients about 4 weeks to see if their hemolytic markers as well as their hemoglobin improves. But typically, in addition to steroids, I'll start rituximab at the same time too. I make sure I check infectious lab: hep B, hep C, HIV, TB to make sure that those infection tests are negative.

But I'll start rituximab and steroids at the same time, whether it's inpatient or outpatient. And the reason why is because previous studies have shown that rituximab in addition to steroids have achieved a higher response at a 1-year mark versus just steroids alone.

But after the 4 weeks, about 3 to 4 weeks, if the patient's hemoglobin hemolytic markers do not improve, that's when I would consider the patient refractory. But currently, there's no standard definition of refractory wAIHA.

Dr. Piatek:
I agree with what you're saying. I mean, I'd also add that some of the data shows to use the rituximab in the frontline setting for patients with more severe anemia, so hemoglobins <8, patients who are mixed or atypical.

So there's a stronger case in that population to use rituximab, but you can use it in any patients upfront. And then typically, you want to see the hemoglobin around 10 g/dL before you start the steroid tapers. And I think one of the big challenges with the treatment of this disease is that although you get this initial good response to steroids, it can be very difficult to taper these patients.

And so that leads to the effort to add the rituximab in the upfront setting. But if you haven't used that in the upfront setting, then you would use that as your second-line agent as you're trying to move past steroids.

Dr. Nguyen:
Absolutely. The challenge, I think, a lot of hematologists face is how fast or slow to taper the steroids.What is your typical approach that you do?

Dr. Piatek:
So the available expert opinion is to taper over 3 to 6 months. I think we've all seen patients who have been on it much longer than that

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or have required rescue or kind of repeated uses of rescue steroids because the disease is so difficult to treat, and there aren't good treatment options, historically, once you move past rituximab.

So, unfortunately, there is an issue with steroid dependence and the associated complications of long-term steroid use in this patient population.

Dr. Nguyen:
Caroline, how do you approach patients with relapsed or refractory high-risk wAIHA?

Dr. Piatek:
So patients who have relapsed disease after initial steroids or those that you're not able to taper off of steroids, you would want to introduce, usually, rituximab in the second-line setting.

If you've already given rituximab in the first-line setting, and it's been a while or some time since that was received, and they responded well to it, then you can rechallenge with rituximab. But once you move past rituximab, there really have not been good options for these patients.

Although splenectomy shows up as a potential option, that's very seldom used in this patient population. There's many reasons to try to avoid splenectomy: the increased risk of infection, it may not be appropriate based on the patient's other medical comorbidities, and it does not play a clear role in patients with secondary wAIHA. So it has really limited utility, and so most people would favor using other immunosuppressants, such as mycophenolate or azathioprine. And then, there was recently a newly approved drug for wAIHA, nipocalimab, which we'll be talking about soon. But one of the big challenges with this, the treatment of this disease, is that, until just recently, we've had no FDA-approved options for the management of these patients, so it's guided often by expert opinion and trial and error.

Dr. Nguyen:
I totally agree with mycophenolate. You know, we've used cyclosporine, cyclophosphamide, azathioprine, among other immunosuppressive agents with varying degrees of success. And it's really dealer's choice after steroids and rituximab. And I think, again, off label for all these medications, but using IVIg as rescue therapy sometimes can be helpful, too, in the past the second line.

Dr. Piatek:
Yeah, I completely agree. Unlike ITP, the response rates with IVIg are lower, so it depends, it really depends on the patient on whether that's going be a useful strategy for them.

Let's wrap up by looking ahead. Anthony, what emerging therapies are most likely to change how we treat wAIHA?

Dr. Nguyen:
Yes. Thanks, Caroline. I think the most promising right now is finally we have an FDA-approved therapy for wAIHA based on the phase 2/3 ENERGY trial of nipocalimab in wAIHA.

So nipocalimab is a fully humanized monoclonal antibody against a neonatal Fc receptor. So the neonatal Fc receptor is a receptor that binds the pathogenic IgG that causes red blood cell destruction and hemolysis intravascularly and extravascularly. So what the neonatal Fc receptor does is it binds onto the IgG and prevents lysosomal degradation of the IgG.

What nipocalimab does is it binds the neonatal Fc receptor so that it cannot bind to the pathogenic IgG. And the investigators in the ENERGY trial—it was a 3-arm trial looking at nipocalimab at 30 mg/kg every 4 weeks, then 15 mg/kg every 2 weeks versus placebo.

And the primary endpoint was durable hemoglobin response. The durable hemoglobin response looks at hemoglobin of improvement >2, hemoglobin of >10, and these findings have to be present for 3 visits or more by 16 weeks.

And in terms of the data of the trial, the trial was a positive trial. The patients who were on nipocalimab every 4 weeks had a 23% durable hemoglobin response versus only 7% in the placebo group. And other secondary endpoints, such as FACIT-Fatigue score, was improved also. The patients who were on nipocalimab were able to decrease steroids compared to patients on placebo.

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Dr. Piatek:
Thank you for reviewing the trial. You know, I think there is a couple other key endpoints that also got at different ways to look at hemoglobin response. So that stringent durable hemoglobin response is important for our patients, and we want treatments that work in a durable fashion for these patients.

Other key endpoints, we're looking at those patients who had a 2 g or higher rise as well as a hemoglobin of 10 or more: so separately also looking at the time to response. And so what we see is that there are a lot of patients who are benefiting from this treatment. And then time to response is also very clinically important in this patient population.

You mentioned the PRO data. So improvement in FACIT-Fatigue is also very important. So we know that there's a large disease burden for these patients related to fatigue. And so any effective treatment needs to also improve the way that our patients are feeling as well. So I think that's a very important finding from the study as well.

In terms of other emerging options, so there are a few other agents that are also being studied. And, you know, what I find interesting about the landscape of clinical trials for wAIHA is just the varied mechanisms of drugs that are being looked at. So there's BTK inhibition, there's CD19 inhibition, and there is BAFF receptor inhibition.

So these are all different ways of targeting B cell and B-cell development. Also targeting the plasma cell is being looked at, so is using anti-CD38 antibodies. And then complement inhibition's also been looked at here. And then, of course, the FcRn inhibition, which is what you were just discussing. So a lot of varied mechanisms, and I think that it's going to be an exciting time to see what happens in these clinical trials and what options we'll have available to our patients moving forward.

Dr. Nguyen:
Thank you, Caroline. And I think one of the most exciting findings of the trial is that some patients did have response by 1 week after being on nipocalimab.

So the rapid improvement of hemoglobin and hemolysis markers is, I think, could be very beneficial to patients who previously had waited anywhere from 2 to 4 weeks for improvement in hemoglobin.

Dr. Piatek:
Yeah, and I think, additionally, the trial looked at reductions in steroids as well.

And so, as we were talking about earlier, that the steroid burden or the time that patients are on higher doses of steroids is another area that is of concern in this disease and something where we need, you know, better therapy so we can get our patients off of steroids, as was demonstrated in this study.

Dr. Nguyen:
And, Caroline, what do you think about the safety data and adverse events data with nipocalimab?

Dr. Piatek:
So I think the safety data was as expected here. I think it's acceptable safety profile with really no increased risk of infection in this patient population.

Dr. Nguyen:
Yeah, which is remarkable since all of our concerns is decreasing immunoglobulin levels and, with most of the adverse events being manageable, including diarrhea and edema, and, I think, those are definitely manageable, especially given the benefit of this drug for patients with wAIHA.

Caroline, how do you incorporate emerging therapies into your treatment approach for patients with wAIHA?

Dr. Piatek:
So with nipocalimab recently approved, the way that it's labeled is that we can use it after somebody's received steroids or so that can

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either be that they're done with steroids or they're still receiving them.

So that means nipocalimab can be sequenced before or after rituximab. When we are talking about other emerging therapies, that would be in the context of a clinical trial. And so for sites that do have clinical trials open to their patients, we'd always encourage clinical trial enrollment so we can learn more about effective therapies in this disease.

With multiple options available for wAIHA, then, just like with other diseases, we would use shared decision-making with our patients to decide on what the most appropriate option is for them. So, for example, if somebody is wanting something that works quickly, nipocalimab would be an option. For somebody who wants a finite course of therapy, rituximab would be an option since that's typically given as 4 weekly doses. Risk of infection would also be incorporated into treatment decisions as well. And the route of administration, the frequency of monitoring, all of this, these types of things would be discussed with the patient to try to figure out what would be the best fit for them.

Dr. Nguyen:
Great. Thank you, Caroline.And I think that a lot of patients do want to decrease their steroid dose and also want to limit immunosuppressants. So I think nipocalimab is a great medication for those and also holds great promise to wean steroids and also decrease exposure to immunosuppressants.

Dr. Piatek:
Yes, I think steroid-sparing strategies are really needed in this disease.

Anthony, brace yourself. We're moving into our lightning round now, so keep your responses quick and pithy, 30 seconds or less for each topic, and you're up first. So what's your take on the first FDA-approved therapy for wAIHA? Ready, set, go.

Dr. Nguyen:
I think nipocalimab holds great promise as a second-line agent for patients who are either steroid dependent or on additional immunosuppressants for their wAIHA.

And I think that the ability to decrease exposure to steroids, improvement in hemoglobin in these patients who have been seeking an FDA-approved and a second-line option after steroids for their wAIHA is really promising, and I think that it holds great promise and paves the way for additional therapies and additional FDA approvals in the future for patients with wAIHA. Which emergent therapies for wAIHA excite you the most, Caroline?

Dr. Piatek:
There's not a specific agent that I'm particularly excited about. I think I'm just excited about the fact that there are multiple agents being investigated now. And so, as we talked about earlier, they have varied mechanisms of action, so I think that that's exciting to kind of see what will really work in this disease.

And it's possible it'll be a heterogeneous picture, and we'll be able to build out profiles of who will respond to one versus another. All right. So what's the biggest barrier to optimal outcomes in wAIHA?

Dr. Nguyen:
I think the biggest barrier in optimal outcomes to wAIHA is that the heterogeneity of the disease. Some patients have severe disease; some people have moderate, mild disease; and some patients have diseases secondary to wAIHA due to underlying, as we mentioned before, lymphoproliferative conditions, autoimmune conditions. And this is, again, a very rare disease, so many trials have failed in treating wAIHA. And finding the right patients that have wAIHA is very difficult. How about you, Caroline? What are your thoughts about remaining unmet needs in wAIHA?

Dr. Piatek:
So the treatment landscape for wAIHA is changing, but the kind of unmet needs in the field have been treatments that work well in the relapse/refractory setting, treatments that work quickly and that have durable responses.

And then, as we've said a couple times, those that are steroid-sparing as well. So a number of challenges in the management of this

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disease.

Well, this certainly has been a fascinating and educational conversation. But before we wrap up, Anthony, what is 1 key take-home message you'd like to leave our audience with?

Dr. Nguyen:
In terms of the treatment of wAIHA, I think the biggest take-home message is when you start patient on steroids, start them on a good dose, usually 1 to 2 mg/kg per day, and also keep them on for 2 to 4 weeks, and don't taper the steroids until you see an improvement in hemoglobin >10 and improving, a trend towards improving hemolytic markers.

And then, when you taper, taper well, taper slowly, and monitor the hemoglobin and hemolysis markers very quickly. And then, if the patients are refractory to steroids, then nipocalimab would be a great option as a second-line option for patients now that it's FDA-approved.How about you, Caroline? What's your biggest takeaway?

Dr. Piatek:
I think, you know, the takeaway is just that the treatment landscape here is changing, and so it's an exciting time to be involved in this field and to have additional options available to our patients. So I'm just excited that there finally are clinical trials to really hopefully address the unmet need for this disease, as it is very difficult to treat in the relapsed/refractory setting and has largely been managed by expert opinion until just recently. And we're hoping to see future improvements in disease outcomes and patients' burden of their disease in the upcoming years.

That's all the time we have for today. Thank you to our audience for listening, and thank you, Dr. Anthony Nguyen, for sharing your expertise and insights. It was a pleasure speaking with you today.

Dr. Nguyen:
Thank you, everyone, and thank you, Dr. Caroline Piatek, for your expertise too, and also for your insights.

MID-TAG
Dr. Piatek:
For those of you just tuning in, I'm Dr. Caroline Piatek, and I'm here today with Dr. Anthony Nguyen. We're discussing the latest therapeutic approaches for warm autoimmune hemolytic anemia.

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