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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Latest Insights into Rare Blood Disorders: Diagnosis and Treatment Strategies

Announcer:
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And now, let’s get started!

Immune-mediated rare blood disorders occur worldwide. However, recognizing and managing these conditions can be challenging. That’s why this podcast explores the latest on acquired thrombotic thrombocytopenic purpura, cold agglutinin disease, and immune thrombocytopenia.

The moderator for this activity is Dr. David Kuter, who’s Chief of Hematology at Massachusetts General Hospital and a Professor of Medicine at Harvard Medical School. Accompanying slides are available for download in the related content section on the program's webpage.

Now in the first chapter of this activity, Dr. Kuter discusses evidence-based guidelines on the diagnosis and treatment of acquired thrombotic thrombocytopenic purpura, or aTTP for short, with Dr. Spero Cataland. Let’s hear from them now.

Dr. Kuter:
Hello, my name is David Kuter. I'm a Professor of Medicine at Harvard Medical School and Chief of the Program in Hematology at Massachusetts General Hospital in Boston. And I'm pleased to welcome you to this activity entitled, The Latest Insights into Rare Blood Disorders: Diagnosis and Treatment Strategies. We're going to be discussing three different topics today: acquired thrombotic thrombocytopenia, cold agglutinin disease, and ITP.

Our first chapter is entitled, Evidence-Based Guidelines on the Diagnosis and Treatment of Acquired Thrombotic Thrombocytopenic Purpura. And we're going to be, as our learning objective here, describing the recent ISTH evidence-based recommendations for the diagnosis and treatment of acquired ITP.

And I'm pleased to introduce Dr. Spero Cataland. Professor Cataland is Professor of Internal Medicine in the Division of Hematology at Wexner Medical Center at The Ohio State University in Columbus, Ohio. And I'll begin with my first question to him, which is: What is acquired TTP? And how is it different from ITP?

Dr. Cataland:
Well, thank you, David. Really a pleasure to be here and talk with you about this interesting topic. I think simply put, acquired TTP is a disorder of widespread microthrombi that occur throughout the body, injuring multiple organs in the microvasculature. It really arises from either a congenital, or in this case we're talking about the acquired form, an acquired antibody-mediated clearance of the

ADAMTS13 protease. So, without that ADAMTS13 protease, you don't get cleavage of these ultra-large vWF multimers into the physiologic sizes. Without that clearance, you can get ultra-large multimers in spontaneous platelet aggregation and microthrombus formation.

Dr. Kuter:
So, in this situation, it's different from ITP in that it's got a thrombotic component to it, which is probably less so than an ITP, is that correct?

Dr. Cataland:
I think you're correct. If I could take the liberty of overly simplifying ITP as a disorder of just platelet destruction, both will be characterized by a significant and severe thrombocytopenia. I think the difference is in how they get there. The ITP is the clearance or destruction of platelets, and in TTP it's the consumption of platelets, so forming the microthrombotic disease that leads to that acquired thrombocytopenia.

Dr. Kuter:
So, thrombocytopenia is a common clinical question to us hematologists that affects about 10% of hospitalized patients, for example. When do you think about TTP in terms of just the platelet count number? How low does it got to be to think about this disease?

Dr. Cataland:
Yes, I remember being taught many years ago that a platelet count of less than 10,000, you should be thinking about TTP, ITP, or a drug-induced thrombocytopenia. And I think we'd like to think about it in that context to start with. Then we start thinking about end-organ injury which might steer you closer to TTP, meaning abdominal pain, nausea, headaches, other findings such as elevations of the LDH and cardiac injury with the troponin. And also keeping in mind the more common things, drug-induced causes; when a patient comes to the hospital with a normal platelet count, and 6 days later they have a thrombocytopenia, we're thinking more of a hospital-acquired thrombocytopenia, or a drug-induced cause rather than something more rare like TTP.

Dr. Kuter:
So, patients with TTP should think about if they've got a thrombotic component, and is the bleeding component equally important? Or is that of a lower priority?

Dr. Cataland:
Yeah, that's an excellent point. I mean, they can certainly have bleeding issues. But I think you want to think about TTP more as a thrombotic disorder. And you're looking more for the thrombotic component of the disease. So, the abdominal pain, the nausea, the confusion, the end-organ injury that goes along with that thrombocytopenia.

Dr. Kuter:
So, some ITP patients, since I take care of a lot, can have ITP for weeks, months, or have no troubles with it. But is there an urgency of distinguishing acquired TTP from ITP?

Dr. Cataland:
Yeah, I think so. I mean, we certainly worry about both in terms of bleeding and clotting disorders. But there's certainly an urgency to diagnose and start treatment very quickly for TTP to avoid sort of catastrophic complications of a delay in the diagnosis and treatment. Certainly, very important to identify quickly and treat it.

Dr. Kuter:
So, if I'm trying to find out if my patient with thrombocytopenia has got TTP, what are the important aspects of the diagnosis? What are the – what's the ISTH evidence-based recommendations for diagnosing this condition? How do I prove that someone's got it?

Dr. Cataland:
So, that’s a good question. And a lot of the guidelines, scoring systems we see really try to distill down how an experienced clinician who sees a lot of patients with these TMAs will look at these patients. And I remember Dr. George telling me many years ago, he spent the first half of his career teaching the pentad of TTP, and he spent the last half telling people to forget the pentad of TTP. The idea being, you don't want to wait for the pentad to be fulfilled, you don't need all those criteria. And we now use thrombocytopenia, fragmented cells without another explanation, and clear end-organ injury as a result of that to really hone in on the diagnosis.

Dr. Kuter:
So, if I had to order a lab set, it would include a LDH, a smear to look at, and then other specific blood tests?

Dr. Cataland:
I think so. I think right off the bat, you need to CBC, you need to look at the smear. I think an LDH is very helpful, very quickly. And I think

your judgment is just as helpful quickly, really thinking about how did we get here? Are there any other explanations? And I've even been fooled a couple of different times, looking at smears when you don't see schistocytes, as you expect. But you don't have any other explanation for a platelet count of 7,000 and elevated LDH in a confused young female or male patient. In those situations, you're still going to go forward with empirical treatment, while you get some additional testing back later.

Dr. Kuter:
Does a negative Coombs test help you make that distinction from Evans syndrome?

Dr. Cataland:
I think so. That's important as well. We talk about, you know, a Coombs test as bringing in autoimmune hemolytic anemia with the ITP. I think that's helpful. I wouldn't necessarily rely on it, but it's certainly helpful in your evaluation then.

Dr. Kuter:
So, what's the role of an ADAMTS13 assay since they sometimes are hard to get or take a while to turn around?

Dr. Cataland:
Yeah, they are sometimes difficult to get. Sometimes are more readily available within 3 to 4 days. I think it has to be remembered that this is still a clinical diagnosis, and ordering this ADAMTS13 activity and waiting for the result is really an accident waiting to happen. If you think enough of the diagnosis being possible to order that ADAMTS13 testing, you really need to ask yourself about your diagnostic or clinical probability of having a case of TTP, as you see reflected in the ISTH guidelines. And if you have a high clinical suspicion, you'll send the ADAMTS13, which will serve to confirm or exclude your clinical diagnosis, but you should start empiric plasma exchange therapy. And then immune suppressive therapy or caplacizumab based upon your clinical suspicion.

Dr. Kuter:
So, it sometimes is hard to read these ADAMTS13 reports because they'll give you an activity level and then they'll tell you whether an antibody is present or not. How important is it to have both components in making the diagnosis or confirming your clinical suspicions of TTP?

Dr. Cataland:
Excellent question. The most important by far is the ADAMTS13 activity, which really will capture all of the inhibitor status, the functional activity you have as measured in vitro. The inhibitor and the antibody titers, the ELISA is looking at antibody on the ADAMTS13, are very important to confirm the acquired form rather than a congenital form. There can be some idiosyncrasies with the testing. But in general, most important is the activity, and the antibody testing is going to help you differentiate acquired versus congenital form to the disease.

Dr. Kuter:
So, if I think someone's got TTP, and the assay comes back 4 days later into my therapy, I've shown that it's 26%, do they still have TTP?

Dr. Cataland:
It's a good question. I mean, we say less than 10%, clearly they have the disease; we'd like to say 20% or higher, probably not. Think about other reasons why it may be low; sepsis, other acute illnesses, liver disease, the rare cases where you may have somebody as a carrier for congenital TTP, but they may have, not normal necessarily, but lower levels of ADAMTS13 activity.

Dr. Kuter:
So, if I've made a clinical diagnosis, and hopefully that ultimately is confirmed by an ADAMTS assay, what's the initial therapy that's recommended for patients with TTP these days?

Dr. Cataland:
Yeah, no, without question, plasma exchange is still the standard of care. It's the initial therapy that you should use with immune suppressive therapy, which typically will entertain corticosteroids and rituximab. The guidelines reflect the early use of rituximab in patients with a higher clinical suspicion. I think if that's, if I'm going to say, what the standard of care is in most institutions, it's going to be corticosteroids and rituximab, both started as soon as possible with plasma exchange therapy.

Dr. Kuter:
So, when it comes to corticosteroids, is dexamethasone acceptable? Or is it only prednisone or prednisolone?

Dr. Cataland:
Yeah, it's interesting that as much as we talk about steroids, the importance of them in TTP, there's really not a ton of data to really

guide us. I think many use prednisone as just as a convention, you've used it over the years. It's easier, if you will, to taper it. There are groups that use dexamethasone pulse up front. I think those questions become less important with the more frequent use of rituximab early on as a good sort of longer-term version of corticosteroid therapy in patients.

Dr. Kuter:
And the rituximab dosing, is it the typical CLL regimen of four doses? Or have we truncated it to a lesser dosage?

Dr. Cataland:
Yeah, there's been some work that's been done looking at lower doses from Washington University and the late Evan Sadler as well as Marie Scully's group in London, I think the standard approach is still four weekly doses 375 mg/m^2.

Dr. Kuter:
And if you put someone on plasma exchange and corticosteroids and you get the rituximab in, how long does it take for a response to be seen with the normalization of a platelet count?

Dr. Cataland:
It's a good question. The plasma exchange is really going to have that more rapid response and it's going to depend on how much antibody you had, the avidity of the antibody, how strong it may be. But within the first 24 to 48 hours, you should start to see a decrease in the LDH, which will then be followed by an improvement and eventually, you hope, a normalization of the platelet count. So, I think when you're looking for a response, it's not just the platelet count, it's the LDH as well. And when you're looking for the plasma exchange therapy to help in your clinical diagnosis to confirm if that's what you're looking for, a drop in the LDH, then followed by rise in that platelet count.

Dr. Kuter:
So, in patients like that who then have a successful discontinuation of plasma exchange, they've got their immunosuppressive agents on board, they're still on corticosteroids, you want to send this patient home, is there a need for other therapies to send them home on? For example, the use of caplacizumab – and we'll come to that in a second, is now part of our armamentarium?

Dr. Cataland:
Yeah, I think an interesting question. I think the most important endpoint that we don't talk about enough is this exacerbation, which is the newest definition. It's the recurrence of TTP in the first 30 days after the last plasma exchange or anti-vWF therapy. And this is a very real clinical endpoint, typically occurs in the first 2 weeks after the plasma exchange or anti-vWF therapy is stopped. And it results in a patient's being rehospitalized, the central line typically been placed back in, and another course of plasma exchange therapy. It's quite common. It happens in 30 to 40% of patients. And it's a very large clinical dilemma. The treatments that we've had: steroids, rituximab, have just not impacted that. And as I said earlier, it's most common the first 2 weeks after discharge from the hospital. And rituximab is probably the most effective immune suppressive agent we know of in TTP, takes 2 to 3 weeks to start to begin to improve that ADAMTS13 activity.

Dr. Kuter:
So, the new drug, caplacizumab, which many of us have not had much experience with, when do you actually use it? Is it only in the refractory patient? Is it in every patient you want to send home? How would you employ it in your practice?

Dr. Cataland:
It's a great question. So, without question, the data really support it in our clinical experience, and I've had extensive experience with it, is very effective and a safe agent in the right hands. Ideally, we'd only use it in the patients who are at risk for exacerbations or at risk for refractory disease; the two most important uses of it or effects of it. Unfortunately, we just can't tell who those patients are up front. We just don't know reliably who it has at risk for exacerbation and who's going to have refractory disease. So, we will typically use it in all patients up front, unless there's concern for bleeding. The mechanism of action, as you know, David, is it binds to A1 domain of vWF and prevents its interaction with platelets. So, it does a great job of blocking the downstream effects of not having protease function to cleave those ultra-large multimers. But again, it does lead to a mild increased risk for bleeding, which is typically manageable, but needs to be considered in patients before we give it.

Dr. Kuter:
And is this a rather costly treatment or not?

Dr. Cataland:
Yeah, unfortunately, it is expensive. And that's I think one of the difficulties that's limited, some of its more widespread use. I don't believe it's the data, or the side effects associated with it. It's quite impressive to use it. And the issue of exacerbations is really more of

a non-issue with the regular use of caplacizumab.

Dr. Kuter:
Well, this brings us maybe to our last but brief set of questions here, which is, you know: Where do you see the treatment of acquired TTP going in the next 10 years? I mean, what's going to change how we treat these patients? Is it universal adoption of caplacizumab or other therapies?

Dr. Cataland:
Yeah, I think really, I think we're seeing the really the acceleration of the treatment and the advances in TTP, which is quite impressive, whether it's caplacizumab or the recent FDA approval for recombinant ADAMTS13 for congenital TTP. And I think what we're seeing is the future is right now. I mean, the caplacizumab has to be emphasized, it doesn't alter the disease, the ADAMTS13 activity or improve it. It really can be viewed as temporizing like plasma exchange therapy. And really understanding that tells you why it makes some sense in two ongoing studies now of the use of caplacizumab and recombinant ADAMTS13 alone without plasma exchange in the treatment of acute TTP. So, therapy started with those individual agents alone, in different studies I should mention, and the use of plasma exchange at the physician's discretion if needed. I think we're going to see some interesting results of the studies that might change how we treat TTP in the future, in the very near future.

Dr. Kuter:
So, it seems like the focus on current research is finding ways to turn off the, or to affect the ADAMTS13 deficiency. How about using more strong immunosuppressive drugs than rituximab, such as a BAF inhibitor or TRAIL inhibitor or neonatal Fc inhibitor to make the antibody just disappear?

Dr. Cataland:
I think that's a great, great, great question and great thought. I think our first cyclosporine study was really taken from an ITP study many years ago. And I think in TTP, there's been a lot of focus on the upfront treatment, the plasma exchange, rituximab. But with plasma exchange, it's hard to reliably do studies to know what effect you're having, there are a lot of confounders. I think one result of having more targeted treatment of TTP, whether it's caplacizumab without plasma exchange or recombinant ADAMTS13 without, is we'll be able to do better at studying immune suppressive therapy. I think that's, along with long-term complications, that's the new area of intense study. What's the best immune suppressive therapy for TTP patients?

Dr. Kuter:
Well, thank you, Dr. Cataland, that was a lovely journey through the new worlds of acquired TTP. Thank you for participating today.

Dr. Cataland:
Thank you, Dr. Kuter, appreciate it.

Announcer:
In the second chapter of this podcast, Dr. Kuter discusses developments in the diagnosis and treatment of cold agglutinin disease, also known as CAD, with Dr. Catherine Broome. Here they are now.

Dr. Kuter:
In Chapter 2, we're going to talk about developments in the diagnosis and treatment of cold agglutinin disease. Our objective here is to explain the diagnosis and management of a cold agglutinin disease to control anemia and reduce fatigue.

And I'm pleased to introduce to you Catherine Broome. Dr. Broome is Professor of Medicine in the Division of Hematology Oncology at MedStar Georgetown University in Washington, DC. And I'll begin with my first question to her. Dr. Broome, what is CAD? What is its basic pathophysiology?

Dr. Broome:
Well, thanks for having me today, Dr. Kuter. So, cold agglutinin disease is an uncommon autoimmune hemolytic anemia. It is mediated by the presence of, normally, IgM autoantibodies, although we do want to remember that occasionally, these cold agglutinins may be IgG or IgA subclass. And what happens is that the IgM recognizes an antigen on the surface of red blood cells, it binds. The binding of the IgM to this antigen, that complex, is going to activate the classical pathway of complement, and we're going to get C3 deposition on the surface of red blood cells. It's the C3 that acts as a really powerful opsonin and drives the extravascular hemolysis; that is a hallmark of cold agglutinin disease. This extravascular hemolysis is mainly taking place in the liver. Not to forget that when the IgM is bound to that red blood cell, there is also the process of agglutination, especially in acral areas where the ambient temperature may be lower than core body. And that can cause a lot of symptoms with regards to circulation in the periphery like Raynaud's phenomenon, etcetera.

Dr. Kuter:

So, my experience is that we see a lot of reports of cold agglutinins that are sent by surgeons and a wide variety of other doctors. Are all cold agglutinins the same? Or are some more potent, as those we might see in a cold agglutinin disease?

Dr. Broome:
So, we do use a titer differential to try to ascertain that this is actually a primary cold agglutinin disease. And in order to make that diagnosis, we generally like to see a titer that is greater than 1:512. Certain people may have a very low titer of cold agglutinins that either related to that very low titer or related to their thermal amplitude or avidity for the antigen are clinically insignificant.

Dr. Kuter:
So, again, to use the word thermal amplitude, I think that falls hard on someone's ears. So, what exactly does that mean?

Dr. Broome:
So, thermal amplitude is really the temperature at which the antibody is most active. And in cold agglutinin disease, there's a wide range. Some of these are only active at very low temperatures, others are relatively active closer to core body temperature. And it's those that are active closest to core body temperature that are going to tend to cause patients the most consistent difficulty.

Dr. Kuter:
So, again, we have some diagnostic issues. I think here what you've got, we have cold agglutinin disease and cold agglutinin syndrome. What's the difference between these things?

Dr. Broome:
So, primary cold agglutinin disease is going to be the presence of these IgM autoantibodies without an underlying driving condition. So, we know that there are infections such as Epstein-Barr, CMV, we know that there are lymphoproliferative disorders, CLL, Waldenstrom's that can also be associated with the production of these antibodies. And when we find a cold agglutinin, or an autoreactive IgM, in association with one of these underlying conditions, we call that cold agglutinin syndrome. And our therapy ought to be directed against the underlying condition.

When we don't find any underlying condition and we meet certain criteria, which would include the presence of this monoclonal population of B cells that we can see on the bone marrow in patients that have cold agglutinin disease, we then term primary cold agglutinin disease, and the therapy should be then directed against the primary cold agglutinin disease.

Dr. Kuter:
So, if I have a patient with a cold agglutinin report that comes back to me, what are the important aspects of the laboratory tests that should confirm the diagnosis? What do I need to do to confirm the diagnosis of cold agglutinin disease?

Dr. Broome:
Right. So, if you have seen a patient who you think has symptoms that are consistent, who comes back with a direct antiglobulin test that demonstrates C3 deposition on the surface of those red blood cells, and you have set your cold agglutinin titer, a warm specimen must be kept warm until it is processed in the laboratory, and you do come up with this titer, I think additional examinations would absolutely include evaluations for infections that we know may be associated with cold agglutinin syndrome, evaluation for underlying malignancies.

And it's really clinicians decision as to how much of that testing you do. For me personally, I think CT scan chest, abdomen, and pelvis is very important. And I also think that performing a bone marrow examination on these patients at the time of diagnosis, and probably at the time of any treatment changes, is pretty important. Because you want to evaluate that World Health Organization classification, you want to work with your pathologist, you want to do the appropriate staining, so that you can differentiate this disorder from other lymphoproliferative disorders.

Dr. Kuter:
So, if I'm going to look at my lab tests from a patient, I have Coombs test, it's positive for complement, I've got signs of hemolysis with an LDH that's elevated and a low haptoglobin, I then have a cold agglutinin titer which is of some issue, I will then do a bone marrow biopsy to show that there's probably a clonal B cell population but not enough to make a diagnosis of lymphoma. Is that how the current algorithm works?

Dr. Broome:
I think that's a very good algorithm, remembering that you also want to throw in there and make sure that you're not looking at an underlying infection.

Dr. Kuter:
And then, as you said, an additional test would be a CAT scan looking for adenopathy, hence lymphoma, a bone marrow biopsy, which I

think I agree is mandatory in all these patients, and probably flow cytometry looking for clonal B cells. Is that the big list of all your evaluations?

Dr. Broome:
Absolutely.

Dr. Kuter:
Great. So, has the WHO classified this now as a unique disease? Or is it just an outlier?

Dr. Broome:
It has. So, the WHO has classified it as a low-grade lymphoproliferative disorder. It has specific markers, including MYD88 negativity that, again, you can work with your pathologist to try to differentiate this particular clone from, say, a Waldenstrom's or other low-grade lymphoproliferative clone.

Dr. Kuter:
So, we probably have skipped ahead of the game here a bit. We haven't talked much about the symptoms that patients with cold agglutinin have. But what are the things that you commonly see in patients who've got cold agglutinin disease? What are the symptoms that they present with?

Dr. Broome:
Well, as you might remember, these are an older population of patients. Generally, you're going to diagnose this in patients that are in their sixth, seventh, eighth decade of life. Many of them are coming with some nonspecific symptoms, right? Maybe a mild to moderate anemia, they are complaining about fatigue, exercise intolerance, shortness of breath, and dyspnea on exertion. You know, some of them will complain about cold-induced acrocyanotic symptoms, but some of them don't complain about the acrocyanosis. I wouldn't pin my hat on looking for acrocyanotic symptoms if you find someone who you think has a hemolytic anemia. I think doing a direct anti-globulin or Coombs test is very important.

Now, under the surface, you know, things that patients don't necessarily complain to us about or that we have only recently associated with cold agglutinin disease, include that they have an increased risk of both venous and arterial thrombotic events. They have an increased mortality when compared to age, sex, and comorbidity-matched controls. They do really report a significant impact on their quality of life. And they also have been demonstrated in a retrospective study to have increased anxiety and depression, again, when compared with an age and comorbidity-matched control population. So, this is you know, not this benign, you are a little bit anemic kind of a disease, but it really is a systemic disorder that is having significant impact on patient's quality of life.

Dr. Kuter:
Is there a staging scheme for patients as to being severe versus mild disease? Because in my practice, I've got some patients who are horribly sick from this, and other patients who have lived blindly for many decades with no troubles.

Dr. Broome:
So, there really isn't a well-established or well-evaluated staging system. We do know that patients certainly can go through periods of time when they may be relatively asymptomatic. We also know that patients can become ill very quickly with exacerbations of the hemolysis that is associated with cold agglutinin disease, particularly in association with any kind of inflammatory stress or infection.

Dr. Kuter:
So, let's switch to how you treat a patient once you've made the diagnosis. I think the first question would be: Who needs to be treated? And the second question is going to be: What are the treatment options?

Dr. Broome:
Well, who needs to be treated I think is a great question. And I think we are still learning and evaluating some of the not-very-obvious-on-laboratory-testing parameters that would gauge who needs to be treated. And I would say anyone who is symptomatic from their disease, whether they are profoundly anemic or not, whether they're requiring transfusions or not, if they have symptoms that you or they are attributing to their disease, I think thinking about treating them would be important.

When we look at how we're going to treat these patients, I think it's important to think about what aspect of the disease is most troubling for them. If the acrocyanosis is the most troubling symptom, then we really probably want to think about something that's going to be more effective at reducing the levels of IgM. And these tend to be B cell-directed therapies. There's single-agent rituximab, and then there's combinations of rituximab plus bendamustine, rituximab plus fludarabine, and then there are other B cell-directed therapies that are under investigation.

If the hemolysis and anemia is really what is the main aspect of this patient's disease, then we have anti-complement therapies. We mentioned how the hemolysis is classical complement pathway mediated, and there is a classical complement pathway inhibitor, sutimlimab, which has been approved for the treatment of patients with anemia with cold agglutinin disease. I think choosing one over the other, again, comes down a little bit to patient preference. Some patients don't want to be on an immunosuppressive therapy, but it also I think should be, at least in part, designed to direct it against what is the main symptom that's bothering the patient.

Dr. Kuter:
So, in terms of this, we've got maybe other therapies that might be thought about as a general hematologist. Would an erythropoietic agent work in this situation just to drive more production to compensate for the destruction?

Dr. Broome:
Yeah, so, erythropoietin agents can be utilized. And certainly, in this older population, there could be some impairment to an appropriate erythropoietin response. But remember that just compensating for the hemolysis with increased erythropoietic activity doesn't necessarily deal with that complement activation. And complement activation really acts as a systemic inflammatory stimulator. So, a lot of times the fatigue is out of proportion to the degree of anemia. And then also we do believe that that complement activation, and the inflammatory nature of it, plays a role in the increased risk of thrombosis.

Dr. Kuter:
So, when it comes to treating these patients, either with sutimlimab-like drug or a chemotherapy approach, what are your major goals in treating a patient? So, what is it you want to achieve? And when do you declare it a success?

Dr. Broome:
Yeah, you know, I think for me, it's really a partnership between myself and the patient. You know, so what are the patient's goals? Generally, they want to feel better, they want to have the energy to be able to do what they would like to do. And so, those are my biggest goals.

In achieving those goals, hopefully, we have improved their anemia. And so, they are able to have a, either no evidence of hemolysis or certainly a much better compensated hemolysis. And along with that, they're going to feel better, they're going to have more energy, they're not going to be short of breath. But I think too, remembering that just giving transfusions or fixing the anemia doesn't necessarily, again, address that complement activation and that sort of systemic inflammation and all the things that go along with it.

Dr. Kuter:
Well, I think that's a very important point, because I think we tend to neglect that this is a systemic disease, not just anemia, or even just an acrocyanosis. Let me ask you one quick question in our remaining 30 seconds here, which is, we've talked about cold agglutinin disease. Cold agglutinin syndrome patients still also have active hemolysis; is there a role for any of these therapies in patients with cold agglutinin syndrome before the chemotherapy for their Waldenstrom's, for example, kicks in?

Dr. Broome:
Yeah, I think that's a really interesting question. And I would say that there are no clinical trial data to answer that question. But there are becoming an increasing number of case reports that do suggest that anticomplement therapy can be utilized and is very effective in initially controlling sometimes that very severe hemolysis that we see while we're waiting for our therapy for the underlying condition to be effective.

Dr. Kuter:
Well, Dr. Broome, I think our time is up here. Thank you for this lovely presentation.

Dr. Broome:
Thank you.

Announcer:
In the third and final chapter of this podcast, Dr. Kuter discusses immune thrombocytopenia, or ITP for short, and the challenges of achieving an enduring remission with Dr. Cindy Neunert. Let's tune in to their discussion now.

Dr. Kuter:
In Chapter 3, we're going to talk about immune thrombocytopenia, the challenges of achieving and enduring remission. Our objectives here are to discuss the mechanism of action, efficacy and safety, and potential place in therapy for emerging ITP therapies.

And I'm pleased to introduce Professor Cindy Neunert. Professor Neunert is a Section Head of Pediatric Hematology at Columbia University in New York, and will talk to us about her interest in ITP. And I'll start this discussion by asking Dr. Neunert, what is ITP? Can

you give us a brief overview of what this disease entails?

Dr. Neunert:
Sure. And for those of you that were listening in Chapter 1, we got into this a little bit, but it's a delight to be part of this. So, thank you for having me here to talk about this.

So, ITP is autoimmune platelet destruction in its simplest form. And, you know, as you know, it to this day basically remains a diagnosis of exclusion. The definition is platelet count less than 100,000 without any other cause. And that's really what we have to hang our hat on. We don't have a lot of fancy tests to help confirm this diagnosis. And it's really based on just the history, the physical, and isolated thrombocytopenia with an otherwise normal CBC and peripheral blood smear.

Dr. Kuter:
So, how do you make a diagnosis? Are any specific lab tests like antiplatelet antibody tests that you do to confirm the diagnosis?

Dr. Neunert:
It would be really great if we had some fancy confirmatory testing, but unfortunately, antiplatelet antibody tests have really not been shown to be very useful. In fact, you know, one of the things that sort of – and this is from work done by your group – one of the only other tests that may be of value is looking at thrombopoietin levels, which can be very, very high in conditions where there's underproduction of the platelets or hypo-proliferation, compared to ITP. But outside of that, it really does remain a diagnosis of exclusion and involves really careful attention, I think, though, to the history and the physical, when looking at the blood under the microscope, particularly as we talk about other etiologies, like TTP and other things that we're trying to exclude in making this diagnosis.

Dr. Kuter:
If I can turn back for one more minute to the pathophysiology, is there any evidence that platelet production is decreased in ITP patients? We've talked about platelet destruction.

Dr. Neunert:
Yeah, so, we now know that these antibodies that are being produced and in their original, you know, we thought they were attaching to glycoproteins on the platelet surface, these antibodies are being recognized by Fc receptors in the spleen, and it was simply a process of destruction. But we now know that these antibodies are also interacting with glycoproteins on the surface of the megakaryocytes. And this is really causing some degree of impaired platelet destruction. And I think it's been really nice to see this story play out, particularly when we get to talk about novel therapies or newer therapies. As we advance our understanding of the pathophysiology, it's been nice to kind of see that in parallel with development of new therapies.

Dr. Kuter:
So, I can summarize if I see a patient with a platelet count of 14,000 and their red cell count's okay, their white cell count's okay, and I look at the smear, they don't have TTP to placate Dr. Cataland, can I assume they have ITP? Am I done?

Dr. Neunert:
So, I think, to some degree, yes, you're done with, in fact, tests to kind of confirm the diagnosis of ITP. I think then the next layer that we haven't really touched on is trying to decide if a patient has what we call primary ITP, meaning ITP in isolation. Or is this ITP in the setting of a more global autoimmune process, such as lupus or inflammatory bowel disease, other conditions in which we can have ITP? So, I think that's sort of then the next step of testing is to decide what additional antibody testing might be helpful, particularly given any patient's symptoms or family history, to really then try to tease out if a patient has primary or secondary ITP.

Dr. Kuter:
So, we'll talk about therapy in a few minutes. But in terms of the evaluation of the patient with the platelet count, for example, of 14,000, which I gave you, what is this disease like as a patient? Are people all bleeding? Or do they have no signs of bleeding? What is it you're worried about in an ITP patient as manifestations of the disease?

Dr. Neunert:
I think we're starting to learn that maybe what we worry about and what patients worry about is a little bit different for ITP. But in terms of bleeding, it's really a heterogeneic. There's not any, at this platelet count, all patients will experience a certain degree of bleeding. Quite fortunate that significant bleeding remains a rare event. There is some link in terms of bleeding with regards to underlying comorbidities or medications that patients may be taking. But in general, there's really not a significant correlation between platelet count and bleeding, except for the fact that the majority of significant bleeding likely occurs under a platelet count of 20,000 or under 10,000. But that's not to say that every patient with that platelet count is going to have a major event.

Dr. Kuter:

So, one of the things that always bothers me is patients with ITP always complain of fatigue, and there's always this history of increased thrombosis risk. Can you discuss those two?

Dr. Neunert:
Yeah, so fatigue is really an interesting, evolving symptom, I suppose, of ITP that patients have been relating to us for some time now. And it links quite closely with their health-related quality of life. I mean, the impact of ITP on quality of life based on quality-of-life measures using the SF-36, for example, patients have impaired quality of life compared to healthy controls, and comparable even to scores with patients who have other chronic diseases such as diabetes. And some of this may be linked to the component of ITP.

There was work done, the iWISh study, and was direct patient surveys of their symptoms and the impact and burden of disease. And that showed that almost 40% of patients with ITP reported some degree of impact on energy levels. And the cause is really unknown. I think we've yet to really establish if this is, in part, worry about the condition. You know, half of patients did report significant worry with regards to their disease course, their platelet counts. So, is the fatigue related to worry and concern and disruption of daily activities? Is it related to living with a chronic condition? Is it medication related? We know that patients on corticosteroids will have impact on sleep patterns and things that can be very disruptive. And then lastly, is there a biological etiology? You know, is this somehow related to cytokines or something very specific to ITP? Some people have even proposed, you know, serotonin levels that are within the platelets and things of that nature as kind of causative. So, I think there's a lot for us still to learn. And I think this is where it's so important for us to listen and learn from our patients.

Dr. Kuter:
So, once you've made a diagnosis of ITP based upon the criteria we've had here, when do you treat? And is steroids the only initial therapy you tend to use.

Dr. Neunert:
So, I think steroids really is the backbone of treatment. And the who and the when to treat, you know, most guidelines would suggest adults receive treatment when the platelet count is less than 20 or 30,000, depending upon which kind of guideline you reference. And it's interesting, you know, in the pediatric side, we really only treat children if they're bleeding, and we don't really have a platelet count cut-off. So, you know, I always say if an 18-year-old gets off the elevator on the seventh floor and they see me in clinic, they may not get treated. If they go a couple floors up to the adults, then they may get corticosteroids. So, there probably is some wiggle room in this, you know, very – this clear cut-off of 20 to 30,000.

And then with regards to the treatment, it's corticosteroids. And whether or not patients get treated with prednisone or short course of dexamethasone really has not shown any difference in long-term outcomes. If anything, maybe there's a slight, more rapid response with dexamethasone, but it also tends to be less well tolerated. I think the biggest message with corticosteroids is not to let patients linger on corticosteroids for an indefinite period of time. And most guidelines are pretty clear; they should be tapered off within at least 6 weeks of treatment.

Dr. Kuter:
So, if steroids are so good that I think the response rates in the 80% to steroids for ITP patients, but unfortunately, it doesn't last for many patients. So, when a patient crashes 2 months later as you wean the steroids, what are the available second-line therapies for treatment?

Dr. Neunert:
So, there's several second-line therapies, and these are the most common that are discussed as second line would be rituximab, which is a monoclonal CD20 antibody that basically works by depleting CD20 B cells and antibody production. It's got about a 60% response rate upfront, but 5 years out, only about 20% of patients will maintain that remission.

But I do think when we talk about second-line therapies, one of the benefits of rituximab is it does have the potential to buy a patient a drug-free remission for some period of time if they do respond. But it does seem to be good in patients that maybe have some underlying positive ANA, or something in that kind of category. And then also, I think there's been some evidence for young female patients having a slightly better response to rituximab. But it's not without its side effects. You know, it's a rather large immune modulator that we're using. So, this is where the thrombopoietin receptor agonists have sort of also become a really good second-line therapy for consideration. There's now three different drugs available. There's romiplostim which is a subq weekly, there's avatrombopag which is a oral agent that can be given daily but even in some patients less than that, and then eltrombopag which is also a daily oral medication. And these essentially work by increasing platelet production, as we talked about earlier with that new knowledge of kind of impaired platelet production by antibodies. And so, the benefit of these is that they're not immunosuppressive; they seem to have very – they're very well tolerated by patients. You know, the unknown is, is there any link to them having benefit of a drug-free remission at some

point? And then I think that's still an area where we're learning as to whether or not they, in any way, modulate the immune system so that patients can taper off and no longer need therapy.

Dr. Kuter:
So, fostamatinib was also approved for treating ITP. Is that in the second line? Or is that a third-line drug for most doctors?

Dr. Neunert:
I think if you ask most doctors, you might get a lot of different opinions on where to position fostamatinib. I think the jury is still out a little bit on whether or not fostamatinib is second or third line. It is certainly in the category of rescue therapy for more refractory patients or for patients who fail initial therapies. But it does have a high side effect profile, particularly with hypertension and pretty poorly tolerated GI side effects. And I think it has lower overall response rates compared to our other options of both the thrombopoietic receptor agonists, as well as rituximab. So again, I think it would maybe depend on the patient, what they've already been on, and which physician you ask in terms of where they would really position it as second line or third line.

Dr. Kuter:
So, an equaly open question is: How do you select between the different three or four, whatever second-line therapies that are there? What is the take-home message as to how you make this decision?

Dr. Neunert:
So, I think, to me, the take-home message is really this is part of where there is the art of medicine. You know, we don't have a lot of high-caliber, randomized, controlled trials putting each of these options side by side. And you know, we didn't even really touch on splenectomy, which was our historical go-to that as a surgical procedure, now reserved mostly for patients who have had ITP for up to a year.

And so, I think it comes down to really understanding what the goals are for our individual treatment for an individual patient. And we can engage in a process called shared decision-making. This is a really deliberate conversation about available treatment options. Those treatment options could also include being enrolled on a clinical trial. But this really incorporates what we know from our medical evidence, our own personal experiences, our guidelines, and tries to match it the best we can with our patient values and preferences.

And in the ASH guidelines, for example, there was a clear statement with regards to second-line therapy, that the choice of treatment really should be individualized and based on the patient's current disease course and characteristics, any comorbidities, age of the patient, their adherence, and support system, and their individual preferences. And this really, when you sit down and put it into clinical practice, becomes a lot of the crux of what we do with these visits when trying to establish what the next best therapy might be.

Dr. Kuter:
So, we have a lot of therapies for ITP. It's interesting that this has changed a lot. Are there any things in the pipeline right now that are in development that excite you about treatments for ITP as we go forward?

Dr. Neunert:
Yeah, it’s actually a very exciting time in ITP. We are getting some new therapies. There are some things in the pipeline that I think are going to be very exciting. These include the Bruton tyrosine kinase inhibitors. You know, Bruton tyrosine kinase is widely expressed in a number of immune cells and is really responsible for B cell maturation, antibody production in our Fc receptor mediated signaling pathways. So, it's a really nice, targeted therapy that makes sense. The problem in the past has been that Bruton tyrosine kinase inhibitors have led to platelet inhibition as well. So, we certainly don't want to give somebody with a quantitative platelet defect a qualitative defect on top of that.

So, rilzabrutinib was designed specifically to address this and not have that platelet inhibition and is becoming a really nice drug to follow the story of our patients with ITP. And in dosing, the current study that's open is the LUNA 3, this is 400 mg, it's taken twice a day. And up to 40% of patients in the original trials had a really nice response, including long-term response. But what I think is most exciting is that the median time to response was 11 days. And this, to me, has been a huge unmet need, is that a lot of these other immunosuppressant medications that we use as third line can take quite some time to have an effect. And again, I think this in part leads to these lingering courses of steroids and tapering and tinkering. So, the faster we can get patients off corticosteroids, the better. And I think patients would agree with that as well.

Dr. Kuter:
So, in our remaining minute, are there any other interesting therapies like neonatal Fc inhibitors or BAF inhibitors that are interesting for ITP?

Dr. Neunert:

Yeah, so the FcRn, neonatal receptor blockers, is another really emerging therapy category that I think is quite interesting. So FcRn is responsible for recycling of our IgG's. So, by blocking this, we're basically blocking the recycling of our antiplatelet antibodies and thereby reducing the amount of circulating antibodies at any given time. The main one in the pipeline right now is efgartigimod. Currently, the results have come out with IV weekly dosing in phase 3 data, where patients receive weekly dosing weeks 1 through 4, and then went to extended dosing of either weekly or every other week, for up to almost 24 weeks. And again, 40% of patients had a platelet count greater than 50,000 four times within the last 12 weeks of the trial. And again, 40% of patients had a platelet count greater than 30,000 within about 7 days. So again, this may fill that need of a more immediate kind of platelet response.

The other exciting thing I think, for both of these is that the adverse events have been really minimal. We haven't seen large signals of new adverse events or significant adverse events related to either of these classes of drugs. And so again, I think, when we talk about unmet needs, you know, both of these are appealing in that sense, as well.

Dr. Kuter:
Great. Well, I think we could talk for many more hours on this topic, given the plethora of new medications, and also maybe spread our discussion to pregnancy at some later stage, but our time is short right now. Thank you, Dr. Neunert, for this lovely presentation.

Dr. Neunert:
Thank you.

Announcer:
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