Immune Thrombocytopenia: The Challenges of Achieving an Enduring Remission
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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 equally 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.