Shruti Chaturvedi, MD:

Hello everybody, and welcome to the CME program on ITP or immune thrombocytopenic purpura. My name is Dr. Shruti Chaturvedi, and I'm an associate professor of medicine in the Division of Hematology at Johns Hopkins University. Today, I'll be covering some clinical research highlights in ITP that were covered at the ISTH meeting in 2025. Here are my disclosures. Also note that this program is supported by a medical education grant from Sanofi.

So what is immune thrombocytopenia? Immune thrombocytopenia, or ITP, is one of the most common causes of isolated thrombocytopenia. We all know that it's caused by antibody-mediated destruction of platelets. All the pathogenesis is somewhat more complex than that. And clinically, it's a diagnosis of exclusion. We really need to rule out all other causes of thrombocytopenia before calling it ITP. Now, the history and physical in certain labs are critical here, but there really isn't a single diagnostic test that applies to all individuals.

When we talk about the pathogenesis of ITP, at the end, it is platelets that are causing platelets to be phagocytosed and destroyed by macrophages, because these platelets recognize antigens... Sorry. When we talk about the pathogenesis of ITP, it is driven predominantly by antibodies directed against platelets and leads them to be destroyed in the reticular endothelial system. When these platelets are phagocytosed by macrophages predominantly in the spleen, they are broken down, and then other platelet antigens are further exposed on the surface and presented to other immune cells, which expands the B-cell repertoire and the repertoire of antibodies. Some of these B-cells also mature into long-lived plasma cells that can continue to make antiplatelet antibodies for a long time. Some antiplatelet antibodies also cause dysfunction of megakaryocytes and may reduce platelet production.

Now, bleeding is the most recognized symptom of ITP and really depends on the platelet count for the most part. The lower the platelet count, the higher the risk of bleeding and in general, we start worrying about bleeding when platelet counts are less than 30,000, but especially when they're less than 10,000. Other things that can affect the bleeding risk are the age of the individual. Older individuals tend to bleed more. Medications, for example, that can compound the bleeding risks, like anticoagulants or antiplatelet agents and then procedures. In addition to bleeding, what's been recognized recently is that patients with ITP also report fatigue and poor health related to quality of life. The pathogenesis of these other symptoms is not fully understood, but it's thought to be due to the inflammatory and autoimmune nature of ITP, as well as potentially a side effect of the medications that we use to treat ITP. Now, let's move to the clinical management. As of today, ITP treatment is really focused on reducing the bleeding risk that comes with low platelets.

Now, factors that contribute to our decisions while treating patients include the extent of bleeding, comorbidities. For example, do they have liver cirrhosis that predisposes them to bleeding from varices, or medications that predispose to bleeding, interventions or surgeries that can cause bleeding, or side effects of treatments? The patient's activity and lifestyle may help you choose a particular therapy, and also the patient's expectations or worries about disease burden. The first-line or rescue treatments for ITP are really treatments that we use when platelet counts are very low and we want a quick response in terms of the platelet count to reduce the bleeding risk. Today, these treatments really look like one of two forms. Either intravenous immunoglobulin or corticosteroids, which could be either prednisone or dexamethasone. Response rates to both of these treatments are about 70 to 90% and really, if a patient does not respond to either of these regimens, it should make us reconsider our diagnosis and look for other causes as well.

The time to response may be slightly faster for IVIG, and then some clinicians will use both together when a very rapid rise in platelet count is required, or platelet counts are critically lower, and there is significant bleeding. Now, many patients, particularly adults with ITP, will respond to IVIG or steroids,

but that response is likely not going to be long-lasting. About two-thirds of adults will transition into what we call chronic ITP. So what do we do when the first-line treatments are not enough when they respond, but don't hold onto the response or stop responding? In general, the second-line treatments come in one of three categories. You have rituximab, which is an anti-CD20 antibody, a thrombopoietin receptor agonist that increases platelet production and then splenectomy that removes the site of platelet destruction. There are certain other treatments that we will mention that are moving into the second-line setting, but we're generally choosing between these three options.

Now, there isn't a clear best option of these three, since they've never been compared head-to-head, and treatment is individualized. Also, when we think about ITP, we think about the different phases of the disease. You have newly diagnosed ITP, followed by persistent ITP, which is generally considered between 3 to 12 months of diagnosis and then chronic ITP that has lasted for over a year. Initial therapy, as I mentioned, is usually corticosteroids or IVIG, with the next line treatment being the thrombopoietin receptor agonist, rituximab, splenectomy and now even sometimes fostamatinib, and there is robust evidence, including clinical trial support for all of these treatments. If patients become refracted to these treatments, then we move on to our salvage treatments, which are a number of immunomodulatory agents as listed here, and there is less robust evidence supporting these. Emerging therapies today are efgartigimod or neonatal Fc receptor antibody inhibitors, rilzabrutinib, which we're going to talk a lot more about, sutimlimab and anti-CD38 or plasma cell-reactive therapies.

It's important to note that while these are listed here sequentially, they are not necessarily used only in these phases of disease. For example, patients, even with persistent or chronic ITP, may receive rescue treatments if their platelet counts fall too low. Now, there are several unmet needs in the treatment of ITP. In the beginning, what we are really dealing with is the steroid side effects and the low rates of durable response with IVIG and corticosteroids. But in later lines of treatment, we have a lack of well-tolerated treatment options for patients who are refractory to second or third-line regimens that will lead to a durable response. Many of these treatments have significant side effects and impact the quality of life as well. So we are really looking for agents that plug these gaps. Let's talk about a case that's going to lead us into some of the abstracts that were presented.

So this is a 38-year-old male who presented with a history of relapse, primary ITP, most recently treated with fostamatinib, and he has a platelet count of 12,000. He still has a response to corticosteroids and IVIG, but as we know, this is not a great long-term strategy, and he has previously received rituximab, romiplostim, eltrombopag, avatrombopag, mycophenolate and cyclosporine. Without responding to these. He would prefer an oral treatment for lifestyle reasons, so where do we go now? Do you consider a splenectomy, rilzabrutinib, lanalamab or daratumumab? I will point out here that rilzabrutinib was approved by the FDA at the end of August. And this is the first abstract that I'd like to discuss. These are platelet responses by international working group criteria for the LUNA3 trial of rilzabrutinib versus placebo in patients with primary ITP, presented by Dr. Ghanima. Now, rilzabrutinib is a novel oral Bruton tyrosine kinase inhibitor that has been used in ITP.

BTK inhibition actually has myriad effects. It affects B-cells and plasma cells by blocking B-cell receptors and inhibiting plasma cell differentiation and maturation. It blocks IgG-mediated activation and phagocytosis in monocytes and macrophages. And these are the two primary types of effects that are active in ITP, but in addition to that, it also affects mast cells and basophils, neutrophils and T-cells that are less relevant in ITP. Now, many people here who also treat cancer will recognize that another BTK inhibitor has been extensively used in CLL, which is ibrutinib. Rilzabrutinib is different from ibrutinib in that it is much more selective in the kinases that it inhibits, and for that reason, it does not have the platelet inhibitory effects that ibrutinib has and also has less class-specific toxicity for BTKs. Now, here is

the study design for the LUNA3 study. This was a multicenter, double-blind, placebo-controlled, randomized phase III trial.

Adults with persistent or chronic primary ITP who had had responses, but not sustained responses to IVIG or anti-D or steroids, were randomized. Their platelet count had to be less than 30,000, and they could be on a stable dose of corticosteroids or TPO receptor agonists when they were randomized. There was a 24-week double-blind period when patients were randomized to either rilzabrutinib or placebo, followed by a 28-week open-label period where patients got rilzabrutinib 400 milligrams twice a day, followed by a long-term extension phase. Now, for the primary endpoint of the study as defined by the protocol, this was a durable response at 25 weeks, defined as a platelet count over 50,000 for over two-thirds of the last 12 weekly visits without requiring rescue therapy. They had a number of secondary endpoints, including the initial platelet count response, use of rescue therapy, et cetera. Here are the baseline characteristics of the study population.

You will note that the median age was in the late 40s. The majority were female in the rilzabrutinib group, as well as the placebo group. Patients had had ITP for a fairly long duration, ranging from about eight years in the rilzabrutinib group to about six years in the placebo group, and this was a very heavily pre-treated group of patients with almost 50% in the placebo group and close to 50% in the rilzabrutinib group having received five or more prior therapies. So this is not the patient who's just failing the second-line treatment. These are patients who've seen several treatments over here. A significant proportion had had a splenectomy in the past, which is about 28% in both groups. To summarize, this is a very typical ITP clinical trial population. In terms of efficacy by the primary endpoint as defined, a durable response at week 25 was seen in about 23% of individuals, but the overall platelet count response was 65%, which is quite high for patients in this line of treatment. The median time to platelet response was about two weeks.

Now, we've talked about the primary endpoint as defined by the trial, but anyone who treats ITP knows, is that if you have a platelet count of 10,000 in an individual, it is wonderful if we can get to 50,000, which was the threshold for the primary endpoint, but many of us will accept and be happy with a rise in platelet count that is not quite as high as 50,000 and which is the international working group response defined as a platelet count that rises over 30,000, which is a range where we're slightly less worried about bleeding complications and at least double from the baseline in the absence of bleeding.

And they define durability as more than 50% of assessments during the double-blind and the open-label periods. Now, here is the durable response rate for the rilzabrutinib and placebo group as per this definition, which is slightly less stringent but is much more clinically meaningful. In the double-blind treatment period, 41% of people in the rilzabrutinib group versus 9% in the placebo group had any durable response. And if you go back down, you see that response rates were maintained really across all classifications, whether they were initially assigned to rilzabrutinib or placebo, the number of ITP therapies they've received in the class, et cetera.

When we look at the median platelet count during the double-blind period, what you're seeing here in the purple line with the squares is rilzabrutinib responders, and you see that the platelet count is relatively stable and gradually increases over time. You do not see significant platelet count responses in the non-responders, which are in rilzabrutinib or placebo, which are the open squares of circles, and you do not see any stability of response in the responders in the placebo group either, which are these peaks that you're seeing. Now, moving on to the open-label period that followed the randomized period, you see a very steady platelet count, which is well above the threshold of response in the rilzabrutinib responders, which is very reassuring.

Now, moving on to other endpoints with rilzabrutinib, it's worth pointing out that an abstract presented at ASH last year showed that rilzabrutinib also improves health-related quality of life versus placebo in

adults with previously treated ITP, and one of the secondary endpoints that improved was also bleeding. So first of all, rilzabrutinib showed a longer duration of platelet count response in all patients, as well as responders, suggesting that there may be a reduction in bleeding even in those that did not have a platelet count response by definition. There was less use of rescue therapy, and the bleeding score at 25 weeks was significantly reduced in patients with rilzabrutinib versus placebo. There were also improvements in fatigue. In terms of the fatigue score, patients in the rilzabrutinib group had an improvement of eight points at week 13 and 4.7 points at week 25, but there were no improvements seen in the placebo group at all.

Now, in terms of safety, most safety events for grade one to two severity versus placebo, diarrhea was relatively common at 23%. There were two severe events. One grade for neutropenia lasting 14 days, but there was no infection and no change in treatment was required, and There was one grade three serious AE of a pulmonary embolism in a patient with multiple risk factors, and this patient discontinued treatment. So in conclusion, there's a high response rate of about 65% in previously treated ITP patients, about a 31% durable response at week 25 by the primary definition from the trial and about 15 days to response. In the second-line setting, there's about a 83% response rate, which I would like to highlight is higher than the response rates reported for rituximab in the same line of treatment, and there are improvements in many secondary endpoints, including bleeding, fatigue and quality of life. Overall, the drug was quite well tolerated without significant class effects, side effects. Next, I'd like to move on to some real-world studies.

The first abstract I'm discussing is real-world outcomes of avatrombopag treatment in patients with primary ITP stratified by prior exposure to TPO receptor agonists. Now, we're aware that TPO receptor agonists have been approved for over a decade. The first approval came in August of 2008 for romiplostim, and we now have three drugs available that are approved for the treatment of chronic ITP. These are romiplostim or Nplate, eltrombopag or Promacta and avatrombopag or Doptelet. Romiplostim, as you'll be aware, is a subcutaneous weekly injection, while eltrombopag and avatrombopag are oral agents. The major differences between eltrombopag and avatrombopag are that eltrombopag has a greater signal for hepatotoxicity and requires LFT monitoring.

And also that eltrombopag has more dietary restrictions around it, because of food interactions, which are not present for avatrombopag, which makes it slightly easier to take. Now, in this abstract, the authors assess the real-world response to avatrombopag in patients with primary ITP classified by those who had received TPO receptor agonists in the past versus those who had not. The data that's not clearly available is the reason to switch from one agent to the other in patients who were previously on other TPO receptor agonists. This was a retrospective multi-site chart review of 177 individuals that predominantly evaluated platelet count responses and steroid discontinuation.

Looking at the cohort, about 117 patients had received TPO receptor agonists in the past and 60 had not, the mean age was slightly older for those that had received TPO agonists at 58 versus 52 and the median duration of ITP was also slightly longer as expected at 2.8 years in those who had received thrombopoietin receptor agonists in the past versus those who had not. However, platelet count responses were really similar if you use a threshold of 30 or 50 or 100,000 in all groups. The only major difference here was that the patients who had not received TPO receptor agonists in the past had a slightly higher complete response rate, which is a response of greater than 100,000.

Steroid discontinuation rates were numerically slightly higher in those who had not previously received TPO agonists, but this was not statistically significant. Shown again, here is the avatrombopag response by prior exposure and you will see that really, in both patients who had or had not received avatrombopag in the past, response rates were quite high with any threshold and there was a higher

rate of steroid discontinuation in both groups, suggesting that avatrombopag has efficacy even in patients who have previously received TPO mimetics and may have a longer duration of ITP.

Moving on to pediatric ITP, this abstract discussed stepwise treatment versus TPO-RA-based second-line treatments for severe immune thrombocytopenia in children. Now, the rationale behind the study is that in pediatric ITP, TPO receptor agonists are considered the standard second-line treatment. However, the study followed patients who were treated in two ways. The stepwise protocol was starting with high dose dexamethasone, which is the standard rescue treatment, moving on to rituximab and then from there, moving on to TPO receptor agonists based on predefined response threshold. This was compared to patients who went straight from dexamethasone to TPO receptor agonists, which is the standard of care. The total study population was 143 individuals.

Now, what they found was that the response rate to remission rate was quite similar in both groups, bleeding rates were similar, and the side effects were actually higher in the TPO receptor agonist group, where you're seeing only 9% side effects in the stepwise group, but around 39% in the TPO receptor agonist as a second-line group. And we had a much, much higher rate of sustained response to treatment at 74% in the stepwise group, and these are the individuals that received rituximab prior to receiving TPO agonists, but no patients in the group that received TPO agonists second-line had a sustained response to treatment. The cost was also significantly lower in the stepwise group, suggesting that the stepwise treatment, where people receive rituximab prior to moving on to TPO receptor agonists if needed, gives patients a chance at a sustained response to treatment, which is expected to be seen in the proportion of individuals who received rituximab and is also quite cost-effective.

Next, moving on to novel treatments, the first study I'm talking about is a pediatric study evaluating the long-term efficacy of daratumumab, which is a plasma cell-directed agent in chronic refractory ITP. This was a single-center study of 11 individuals, and daratumumab was given weekly. Follow-up was up to nearly 400 days. The initial response rates were quite high at 81.8%, as was the response at three months, which was about 91%. 43% of individuals had a sustained response at six months, and about 66% at 12 months. The bleeding score significantly reduced in most individuals, and there was no bleeding at three months. For patients who relapsed after this regimen, three out of four responded when retreated and overall, it was safe and well-tolerated with minimal side effects. While 82% did have adverse events, these were mild to moderate and restricted to the first dose, predominantly infusion reactions or allergic reactions.

Now, daratumumab is also being evaluated in a phase II efficacy and safety study in adults with refractory ITP. In this protocol, there is a three patient safety run-in followed by two dosing cohorts, receiving either 8 or 10 doses of daratumumab for 8 or 12 weeks. The primary endpoint is two consecutive platelet accounts over 50,000 at week 12 for the safety run-in cohort in the first cohort and evaluation at week 16, so essentially four weeks after the last dose for both cohorts. 12 weeks for cohort one and 16 weeks for cohort two. This is, again, a very typical ITP clinical trial population with a median disease duration of about 60 months, a median baseline platelet count of 17,000 and four median prior therapies. The overall results here are that 52% had met their primary endpoint. Again, 50,000 platelets at two consecutive platelet count assessments. Sustained response at week 24 was seen at 38% with a median response duration of over 350 days.

There were a couple of grade three adverse events in two patients. One was an infusion reaction, and the other was infection with COVID-19. Immunologically, it was assessed that CD38 cells went down as expected with a reduction in IgG levels, which is also effective. In terms of response rates and duration of response shown in this graph, you're really seeing that there's a response of about 66% of the safety run-in cohort and about 44% in both the other cohorts. Sustained response was seen in 44% of cohort one and 33% in cohort two. Shown on the right-hand is a Kaplan-Meier curve showing the duration of

response, and it does appear that the response duration is relatively sustained in patients who have a response. Future results of plasma cell-directed therapies are eagerly awaited, and we already have in this abstract the final results of the phase two trial of mezagitamab, another plasma cell-directed agent in chronic ITP.

Now, this trial assessed the efficacy, durability of response and quality of life with mezagitamab in chronic or persistent ITP. It's a randomized, placebo-controlled phase II trial where patients received weekly mezagitamab at one of three doses. 100, 300 or 600 milligrams for eight weeks. The bottom line is that all doses showed favorable safety, background ITP treatment was permitted in this trial, and this agent improved platelet count response duration and ITP-related quality of life in what appears to be a dose-dependent manner. So looking at the results over here with the 100, 300, 600 milligrams of mezagitamab or placebo, there was a mean increase in platelet count duration versus placebo of about five weeks with a 100 milligram dose, seven weeks with a 300 milligram dose and 9.6 weeks with a 600 milligram dose. All of these doses showed clinically meaningful changes in a quality-of-life instrument, which is the patient assessment questionnaire in ITP.

The duration of platelet count response on the right-hand side of the graph is as I've just mentioned, and I'm showing you here, the ITP patient assessment questionnaire results from changes from baseline to week 16, where the red bars here are all doses combined of mezagitamab, and most of these patients cross the minimally important difference over here. We don't see any meaningfully important improvements in patients who were in the placebo group. So to summarize, in the ITP updates from ISTH, rilzabrutinib demonstrates durable responses based on International Working Group criteria, which are clinically meaningful, particularly in patients who have received fewer prior ITP treatments. Avatrombopag appears to be effective regardless of prior TPO receptor agonist exposure. Responses that will be considered complete responses, over 100,000 platelet counts, are seen in patients who are naive to the TPO receptor agonist for the most part.

A stepwise response-guided protocol offers comparable efficacy to TPO receptor agonists with fewer adverse effects, higher off-treatment response rates and reduced cost. Daratumumab shows strong initial and three-month efficacy in pediatric chronic ITP. For patients who do relapse after this regimen, retreatment appears to be effective. In adult individuals with persistent or chronic ITP, 52% response rates were seen with daratumumab, with response lasting several months with good tolerability. And finally, mezagitamab extended platelet count response duration and improved quality of life in a dose-dependent manner, again, in adults with chronic ITP, but additional results are required. Of these treatments, rilzabrutinib was recently approved, and we await real-world evidence studies in this drug as well.

Thank you so much for joining us, and have a great day.