Practical Hematologist

Clinical Commentary: Diagnosing and Treating Patients with PNH

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Dr. Griffiths: Good afternoon, everyone. Thank you for your attention.

The first one I'm going to ask of Dr. Weitz, do we currently have any criteria for patients failing eculizumab and when do we decide to stop therapy, Dr. Weitz?

Dr. Weitz: Well, number one, you need to decide what do you mean by failing? If you're saying that the patient's LDH is not coming down, or they're still transfusion dependent, so it depends on your criteria. It's very rare to see that the LDH has knocked down with the adjustment of eculizumab or ravulizumab dose, especially with ravulizumab. Very difficult, very rare to see that the patient hasn't responded, but there are a few patients, some of them have a polymorphism in C5 that should be very evident very early within the first month or so. There are only a handful of those patients.

Second, if the patient remains transfusion-dependent, that's very worrisome, and especially if they have a high retic (reticulocyte) count, those patients definitely should be considered for an alternative therapy. The question is, what about those patients who are in between, they're not transfusion dependent, but they're still anemic. If they're feeling bad, they may be candidates for switching to an alternative therapy.

Dr. Griffiths: Dr. Weitz, at this time, the alternative therapy that we routinely use is pegcetacoplan.

Dr. Weitz: Yes, that's the only other approved complement inhibitor. Anybody who has a persistent anemia in the clinical trials, they used a cutoff of hemoglobin of 10. Anybody who's still symptomatic with an anemia or those who are transfusion dependent definitely should be considered for switching, but you should also make sure they have an adequate retic count and that they have C3b on their cells.

Dr. Griffiths: Yes. I think this is a question about eculizumab. There are some people who have breakthrough at the end of the dosing interval. For those patients, as we discussed at length in our previous presentation, sometimes it's worthwhile to consider switching to a longer-acting form of a C5 inhibitor like ravulizumab and those patients can derive benefit from that. Would you agree?

Dr. Weitz: Yes, absolutely. You can identify that if the LDH is normalized on day eight, and then it pops up at day 15, that is suggestive that they're breaking through because eculizumab has a very short half-life. Going to ravulizumab, the C5 levels are suppressed immediately, and they

stay down for the full eight weeks. I do have a few patients who break through right at the end of their ravulizumab dose at week eight. It's within the label, they get their dose every seven weeks.

Dr. Griffiths: Yes. I have a few patients like that too. The next question here that we received was, do patients stay on treatment for life. I have a couple of patients. I'll just start and I'll ask you what your opinions are. I've had a couple of patients where we serially monitor their PNH clone size, and I've read some patients where that clone has diminished to the extent that it's no longer clinically relevant or significant.

I had one patient who had an antecedent history of an aplastic anemia who received immunosuppressive therapy, had a really nice response, but then had a pretty large PNH clone, and then sequentially, evaluation of the PNH clone showed decrease in this size to less than 5% with no evidence of ongoing intervascular hemolysis. We made the decision to take him off therapy and he's doing well, and we continue to monitor his PNH clone size, but he's been able to stay off. Do you have similar stories?

Dr. Weitz: I have only one patient who was not on treatment, but her clone size decreased from 40% to 20% as her marrow failed and then when she recovered, she recovered mostly with more normal cells and never went on treatment. I haven't had any patient on treatment whose clone size has decreased. I know the people at LEADS have patients in whom the clone size decreased. Almost all of those patients they had to put back on treatment when they stopped.

Dr. Griffiths: I actually have a patient who I recently elected to hold treatment. He had a history of aplastic anemia as a child, and then had started on eculizumab for years and years and was on since its initial approval. Then more recently, his clone size now has fallen to less than 10%. He really wanted to come off. We've been monitoring. We continue to monitor him every six months and follow his clone.

Dr. Weitz: What was his clone when you started him?

Dr. Griffiths: I didn't start him again. He started before I graduated from my residency, but at that time he had a very large clone and he had clinically Coca-Cola-colored urine, and the current breakthrough hemolysis. For him, it was wonderful. He's now in his late 40s. He was originally diagnosed as a kid and he did really well. Initially when I started seeing him his clone size was in the 60% to 70% range, and he was doing great.

Then recently his clone size has fallen. It's now less than 10% and he has still a degree of bone marrow failure. He stays on low-dose prednisone, five milligrams, but he actually has platelets running at 100. His hemoglobin runs in the 11-gram range right now, and his white count is stable he looks great and feels well, and is happy to be off therapy.

Dr. Weitz: Well, I think there are patients like that, and we know that patients with PNH can evolve out of aplastic anemia and aplastic anemia can evolve from PNH so they can go in and out. You just need to monitor the patient.

Dr. Griffiths: For me, what that speaks to is the importance of the serial monitoring, a standing order on those patients, and how important it is to be aware of how patients are feeling and to take clinical history like that.

The next question is, are there any issues to be aware of when switching patients from eculizumab to ravulizumab. I think probably, Dr. Weitz, you have a lot of experience with this. I've done a couple, but I would love to hear what you think.

Dr. Weitz: Yes. We haven't had any issues. I have had a couple of patients who did not do as well with ravulizumab as they did with eculizumab, and these patients were very heavily C3b loaded and they have since gone onto other therapies. The vast majority of patients, it's very easy. You just start the patient when they would be due for their next eculizumab dose, you start them on ravulizumab, you load them two weeks later you put them on the maintenance dose and most of them never look back.

Dr. Griffiths: How far away do you think we are from an oral agent for PNH?

Dr. Weitz: Well, the factor B trial has been completed, so that's being adjudicated, and I suspect next year we will see the factor B available. The factor D was an overlap trial. My own personal feeling is I don't think anybody wants to take two drugs. They're working on a different formulation for that. It can be standalone, and the BioCryst factor D which is standalone hit a little roadblock because of some toxicity. That's on hold or just resuming now.*

**On August 04, 2022 it was announced that the FDA lifted its partial clinical hold on BCX9930. Enrollment resumed in global clinical trials under revised protocols at a reduced dose of 400mg twice daily.*

Dr. Griffiths: Okay. Potentially sometime next year, we hope.

Dr. Weitz: I think so.

Dr. Griffiths: Okay. Then the last question is when should we consider bone marrow transplant for PNH?

Dr. Weitz: There aren't any firmer fixed rule, and you do a lot more bone marrow transplants than I do, but my rule of thumb is number one, if they are aplastic anemia with a PNH clone, you are going to treat the aplastic anemia. If they are not responding to immunosuppressant therapy and they have a large PNH clone, that's something to consider, to consider bone marrow transplant because the aplastic anemia is the primary event.

Second, if they're very young, they will have a lifetime of this disease. Why do we want to go there? I think in very young patients, I would be much more aggressive in pursuing a donor for this transplant patient if they have AA, but also if they have hemolytic PNH. Finally, if they have recurrent thrombosis in spite of treatment and in spite of anticoagulation, which is extremely rare, extremely rare, then they would be considered candidates. I think the anti-thrombotic effect of complement inhibition is very dramatic and it's not likely that these patients are going to progress through.

Dr. Griffiths: Yes, I currently have a patient in our practice who's been really challenging and has had a lot of breakthrough hemolysis and continues to have a lot of problems. Had a pretty extensive thrombosis at initial presentation and continues to have a lot of problems and so she's relatively younger, relatively fit and so she continues to be transfusion dependent, continues to have episodes of breakthrough hemolysis and so in her case, even though I hate to do it, I think we're strongly considering a bone marrow transplant.

But again, I would agree it's relatively rare. I had a patient who had a history of aplastic anemia as a child, who then developed PNH and was maintained on complement inhibitor therapy for a long time, did well, but then developed abnormalities in the bone marrow showed, although he did not have MDS overtly in the marrow but he had developed a clonal cytogenetic abnormality and so in him, we took him to transplant just to fore-stall the potential for development of a secondary hematologic malignancy.

Then I had another patient who again, had very profound, progressive cytopenia. Had received several courses of immunosuppressive therapy and had really progressive PNH as well and so we took him to transplant. He's done well with a haploidentical donor.

Dr. Weitz: Yes, we've done a couple. One had MDS and because she had underlying MDS with some cytogenetic abnormalities, we felt her risk of progressing was higher. Progressing to leukemia or MDS and she had a sibling match, identical match. She's done very well. We've had a couple others. We did a couple of haploidentical, and one died of a fungal infection which was very unfortunate, but the others have done okay, so it's not without complications. The biggest issue was finding adequate donors but with techniques for transplant today, they're much safer than they were five years ago.

Dr. Griffiths: Yes, I think there's also some nice data from the group in Washington state suggesting that using P5 inhibitor therapy right up to the time of transplant seems to mitigate a lot of the previous problems that we had in the past with graft versus host disease in people with PNH. I think there are case series that showed very, very high rates of GVHD and people who active hemolysis at the time they went for transplant.

I think the one nuance from my practice is that I always make sure that people are early post-treatment when they go for their transplant so that they get their C5 inhibitor the day before they go for admission for their conditioning, to try and make sure they minimize complement activation at a time when their bone marrow production is likely to be involved with PIG-A deficient cells. Would you agree?

Dr. Weitz: Yes, I think the other thing is that there's a high incidence of thrombosis with preparatory regimens. If you don't take them through on complement inhibition and now with ravulizumab all they need is one dose and it lasts for eight weeks, so they're going to have recovered by then.

Dr. Griffiths: Right. That's exactly the point.

Before, what I used to do is I would give them eculizumab through the first 90 days of therapy and continue with eculizumab and now I just give the ravulizumab the day before to get ready.

Dr. Weitz: Right.

Dr. Griffiths: Okay, fantastic. All right, thank you so much for your attention today. I hope you felt that this session was valuable.

Dr. Weitz: Thanks everyone.