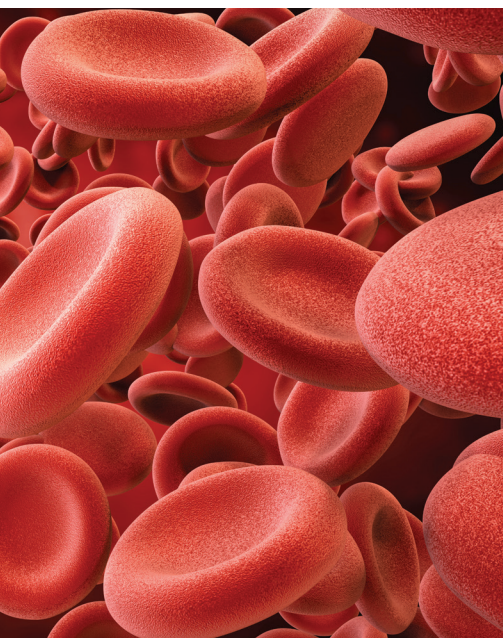


# Selecting and Sequencing Ruxolitinib, Other Treatments in Chronic GVHD



**A**t an *Around the Practice* program hosted by CancerNetwork®, a panel of experts discussed symptom assessment and the selection of treatment options in patients with chronic graft-vs-host disease (GVHD). They reviewed these topics in the context of a clinical scenario involving a patient with acute GVHD. The panel was led by **Nelson J. Chao, MD, MBA**, a cellular therapy specialist and stem cell transplant specialist at the Duke Adult Blood and Marrow Transplant Clinic in Durham, North Carolina.

The panelists included **Hana Safah, MD**, a professor of clinical medicine in the Section of Hematology and Stem Cell Transplantation Program and the Leukemia and Lymphoma Programs at Tulane University School of Medicine in New Orleans, Louisiana; **Erin Kopp, NP**, the director of advanced practice and a nurse practitioner at City of Hope Comprehensive Cancer Center in Duarte, California; and **Catherine J. Lee, MD, MS**, an associate professor in the Clinical Research Division at the Fred Hutchinson Cancer Center in Seattle, Washington.

**SAFAH:** There are options that may also help patients if ruxolitinib fails. Some of my colleagues use ibrutinib [Imbruvica]. I'm not as much of a fan of ibrutinib, though it is an option. It has been studied in patients, and it did show benefits, especially if a patient has only skin GVHD. ROCK2 inhibitors are a good third-line option in patients with disease progression following JAK inhibitors. I also continue extracorporeal photopheresis [ECP] in these patients, especially those with skin GVHD.

**KOPP:** If a patient is starting to show that they may become steroid refractory or dependent, we work them up for clinical trials before we get [to the treatment phase], because clinical trials are an important option to observe. For centers outside of that space, the referral process should start early because clinical trials require screening, slots, and time. We start that concurrently. If we are in a situation where ruxolitinib or any other second-line options are not panning out, we already have the clinical trial potentially available.

**CHAO:** Does anybody have a favorite treatment option?

**LEE:** I'll still use rituximab [Rituxan] or low-dose weekly methotrexate to see [whether] it helps. I've seen rituximab work in the very refractory setting, particularly for oral chronic GVHD. I have not had much luck with very advanced ocular or sclerotic chronic GVHD,

## Treatment Options Following Progression With Ruxolitinib

**CHAO:** Ruxolitinib [Jakafi] is approved as a second-line treatment for GVHD based on the phase 3 REACH3 study [NCT03112603].<sup>1,2</sup> If treatment with ruxolitinib fails, what would you do?



**Nelson J. Chao, MD, MBA**  
 Duke Health  
 Durham, NC



**Hana Safah, MD**  
 Tulane University School  
 of Medicine  
 New Orleans, LA



**Erin Kopp, NP**  
 City of Hope  
 Comprehensive Cancer Center  
 Duarte, CA



**Catherine J. Lee, MD, MS**  
 Fred Hutch Cancer Center  
 Seattle, WA

## PATIENT CASE

- A 52-year-old woman with B-cell acute lymphoblastic leukemia was treated in a clinical trial until a minimal residual disease–negative complete response.
- She received fractionated total-body irradiation, etoposide, and matched sibling donor allogeneic hematopoietic stem cell transplantation.
- Tacrolimus/sirolimus was given for GVHD prophylaxis.
- She was diagnosed with acute GVHD skin stage I, upper gastrointestinal (GI) stage I, and lower GI stage II.
- This was resolved with corticosteroids at 1 mg/kg per day.
- After day 170, she presented with diarrhea 5 times a day, anorexia, and elevated liver function test. The patient also reported tightness around mouth and in the ankles.
- She received a corticosteroid equivalent of 1.5 mg/kg per day for 2 weeks.
- The patient returned to clinic with an increase in diarrhea and was now reporting nausea/vomiting.
- Steroids were increased to 2 mg/kg per day and the patient was admitted due to dehydration and weakness.

although there are reports of rituximab having activity in the setting.

**SAFAH:** Rituximab can be helpful. I sometimes add rituximab early in patients with severe skin GVHD. That's one option. Targeting the plasma cells in patients with progression is another. I've used proteasome inhibitors with minor success. They do not work by themselves, but they can add to the treatments available, whether it's rituximab, [ECP], or antithymocyte globulin. However, there is nothing that will always work. Clinical trials are always important to have. [However], when they fail, it becomes a question of: What is available for us, and what can the patient receive? [At this point], it depends on the clinical status, the comorbidities, and the toxicities from the options available.

**CHAO:** There's the phase 2 AGAVE-201 trial [NCT04710576] with axatilimab that is targeting the monocytes, which is potentially another mechanism.<sup>3</sup>

**CHAO:** What do you think about this situation?

**LEE:** I feel horrible for the patient. This is an unfortunate situation, and it is an example of when patients are released back to their homes, they may not be under close supervision before returning with these severe symptoms. The case

study brings up a couple questions. When the patient developed acute GVHD, it was treated successfully with corticosteroids. The first questions that come up in my mind are: What was going on with the tacrolimus and sirolimus [Rapamune] at this time? Did the patient just stop taking her medications, or had she been weaned off? Regardless, she does present around month 6 with these GI symptoms, elevated liver function tests, and signs of chronic GVHD as she's reporting tightness around the mouth. This needs to be treated urgently.

At this point, I would have admitted the patient into the hospital and started high-dose steroids, as what was done here. I would have started at 1 mg/kg per day, thinking that this might be acute or chronic GVHD and knowing that some other treatment options take a little longer to take effect. I would have started corticosteroid equivalent at 2 mg/kg per day and watched her carefully. If she had not responded by day 5, I would have added a second-line agent and started tapering off the corticosteroids. I don't find a reason here to increase the steroids to 2 mg/kg after someone doesn't respond to 1.5 mg/kg. The patient was left too long on this 1.5-mg/kg per day dose.

**SAFAH:** I agree. I would have been giving the higher dose earlier compared with what was done here. I evaluate these patients very early on. If there is no evidence of response by day 5, or if they're progressing by day 5 and there is no evidence of response by day 7, I elect to go to a second-line treatment rather than increasing the dose of steroids as such.

**KOPP:** This is an excellent representation of the type of patients we receive and the questions that often come with them. If they're not continuing to receive care in the institution in which they underwent a transplant and there are changes to their immunosuppressive regimens, steroids, or presentation of symptoms, we don't always get the full report of what happened. So, patients do show up on my doorstep presenting like this. One thing we need to focus on is how often we're monitoring our patients at critical milestones. When you initiate steroids, the concept is that the patient needs to be closely followed for 3, 5, or 7 days because we can identify—sometimes as early as 3 days—whether a patient is responding to the corticosteroid dose.

I'm hoping this illustrates the challenges that many physicians and other health care professionals have when working with a patient like this. The onus is on everyone who interacts with the patients to say when there's a new symptom and where there's a change in something that we do. Additionally, the patient sometimes must advocate for themselves and say, "How can I see you in another week?" Or call their transplant physician or the long-term care clinic so we're aware of it sooner rather than later.

### Organ Involvement With Ruxolitinib and Using Steroids

**CHAO:** Given our earlier discussion, this patient's condition is not getting better, and ruxolitinib is the drug we would probably all pick to treat her.

**SAFAH:** I agree with you. Ruxolitinib is approved as a second-line therapy in patients who are refractory to steroids.

This patient would be a very appropriate candidate for such a treatment.

**CHAO:** Does it matter which organ is involved in terms of outcomes?

**SAFAH:** When you look at ruxolitinib in the REACH3 trial, the benefit was seen across all organs. We might combine it with other drugs. We can add rituximab, but we need to be careful [because] it may cause immunosuppression. We need to be careful of the risk of infection, especially when we're adding JAK inhibitors. The risk of whether there may be viral reactivation or other infections should be considered when combining ruxolitinib with other immunosuppressants. I prefer to take it slowly. Again, I know benefits have been seen across all organs on the trial.

**LEE:** We know that in the REACH3 trial for acute GVHD, the responses and the duration of response [DOR] were not so great among those who had severe gastrointestinal involvement. This leads to the unmet need that we are still facing, which is understanding what therapy may fit best for a particular organ. This is an area of research that will help guide treatment for different manifestations of GVHD if we can identify and develop biomarkers.

**CHAO:** Do you taper patients off steroids if you have ruxolitinib as an option? What would you do if someone is refractory?

**LEE:** We would taper off the steroids in someone who is refractory. This is also very dependent on the institution. Fred [Hutchinson Cancer Center] has a long history of using steroids and being a little slower on the taper, but other institutions may feel comfortable in terms of rapidly tapering off the steroids.

**KOPP:** My experience is that we are less excited about tapering the steroids even when it seems that patients are refractory. There's the fear that if you see some effect and then take the steroids away, the disease will flare even more. There's a reliance on keeping those steroids as you add ruxolitinib or any other agent on top of them. With any oral agent like ruxolitinib, there has been hesitancy to use it with patients who have GI presentations.

With the REACH studies, there doesn't seem to be an issue with absorption and utilization unless we know there's a significant issue with a patient's absorption. However, there is efficacy to a certain level. That's where I think we start combining steroids with ruxolitinib, which may give the effect but not the DOR. We may then add another agent if we're talking about different organs.

What I have noticed in the [past] 5 years is that the addition of agents has become more intentional. People are looking at the etiology, the drug's mechanism of action, the affected organs, and the research involved. It's a complex process. Before, I would describe practice as a dartboard where you just throw everything at it and see what sticks. Now, there are a lot of ingredients, and we're all more experienced with how it will affect the overall outcome.

### Moving Forward

**CHAO:** Are there any drugs coming down the pipeline that you're excited about?

**LEE:** The field is exciting to look forward to when it comes to more combinational therapies, as we are seeing that combinations of drugs with different mechanisms of action may help control GVHD and perhaps improve it by targeting different biological pathways. I have used a combination of ruxolitinib and belumosudil [Rezurock], and I know some centers have initiated clinical trials of using these 2 drugs in refractory chronic GVHD.

**SAFAH:** In practice, many of us have used ruxolitinib and [belumosudil] together. Some of us have used it in patients who are refractory to one or the other. I've also used them in patients who have severe chronic GVHD and were not going to be maintained on only 1 drug. I'm asking my colleagues now, and I've requested that we start publishing the data on patients who have received the combination and have done well so that our other colleagues can do the same. Belumosudil's safety profile is not bad. On the other hand, the JAK inhibitors do very well, and they

have a nice mechanism for controlling inflammation and potentially fibrosis. Adding them together can benefit patients. We can do it in the refractory setting. Maybe we should start looking at earlier lines, and maybe we can skip steroids. Other than that, I think clinical trials will be best, but we don't have many other options at this point.

**KOPP:** For GVHD, the seeds are planted for early settings in transplant. For post-transplant regimens that include cyclophosphamide, there is a lot of focus on identifying [whether] a patient has acute GVHD or multiple risk factors. There's been a foundation set with biomarkers. What we do with them next may involve the concept of precision medicine in acute and chronic GVHD to meet the needs of the patient systemically.

I've also seen a growth in supportive therapy. For the patient, the fact that we can manage these symptoms while we're treating the underlying process is probably the biggest development that patients are excited about. If patients have skin that feels like it's peeling off and you have 5 more agents now that may treat them topically, that's a huge win as a patient. The same thing applies to oral sloughing. The inability to brush your teeth with toothpaste is something that patients bring to us, as well as needing to wear sunglasses outside at night because their eyes are so dry. The growth in supportive therapy regimens is also something that needs more research because it's important to the patients alongside treating the underlying cause. ■

### References

1. Incyte announces FDA approval of Jakafi (ruxolitinib) for treatment of chronic graft-versus-host disease (GVHD). News release. Incyte. September 22, 2021. Accessed September 11, 2023. <https://bit.ly/3PzZsVt>
2. Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med*. 2021;385(3):228-238. doi:10.1056/NEJMoa2033122
3. Syndax and Incyte announce positive topline results from the pivotal AGAVE-201 trial of axatilimab in chronic graft-versus-host disease. News release. Syndax Pharmaceuticals. July 24, 2023. Accessed September 12, 2023. <https://bit.ly/463K5pM>