Expert Answers to Common Questions for Who's at Risk?

Preventing and Managing Tumor Lysis Syndrome and Neutropenia in CLL

Matthew S. Davids, MD, MMSc: Hello, and welcome to this educational activity entitled, *Who's at Risk? Preventing and Managing Tumor Lysis Syndrome and Neutropenia in CLL*.

I'm Dr. Matthew Davids, Director of Clinical Research in the Division of Lymphoma at Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School in Boston.

First, a disclaimer and disclosure indicating that we may be discussing off-label use of approved agents or agents that are in development.

With regard to learning objectives, upon completion of this activity, participants should be better able to: Identify patients with chronic lymphocytic leukemia (CLL), who are at risk for developing tumor lysis syndrome (TLS); to implement appropriate prophylactic measures for patients with CLL based on risk for the prevention of TLS; to develop strategies for the early identification, monitoring, and management of patients with CLL who develop TLS, based on current guidelines; to employ approaches to assess and manage neutropenia in patients with CLL.

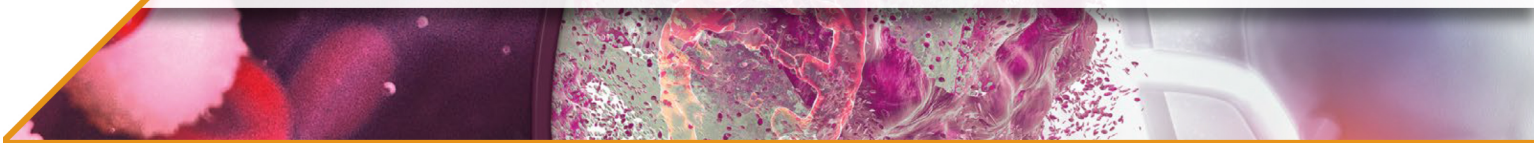
This activity will provide my answers to questions asked by clinicians during a recent CME-certified live webinar series on TLS and neutropenia in CLL, which are categorized here. We saw that close to 80% of the questions were treatment related, and interestingly, a little over 10% of the questions were related to p53 mutation status and lymphadenopathy. Of the treatment-related questions, nearly half were related to venetoclax, the Bcl-2 inhibitor. Nearly one-fourth were related to inhibitors of Bruton tyrosine kinase (BTK inhibitors), and a little over 10% were related to rasburicase.

So the questions I will be answering today are: 1) Just at a basic level, what is tumor lysis syndrome, as a review; 2) Do you withhold venetoclax during TLS treatment, and when do you restart, and at what dose? Do you have to ramp up the venetoclax dose to 400 milligrams if the patient is having an excellent response to a lower dose of venetoclax? When do you feel it's safe to discharge patients during the venetoclax ramp-up? And for a high-risk TLS patient, would you readmit for a second dose of venetoclax ramp-up to 50 milligrams?

We'll also cover rasburicase prophylaxis. Can rasburicase be given in the outpatient setting in a prophylactic manner?

Expert Answers to Common Questions for Who's at Risk?

Preventing and Managing Tumor Lysis Syndrome and Neutropenia in CLL



Neutropenia is also an important issue in patients treated with venetoclax plus obinutuzumab, and therefore I wanted to highlight some additional questions about neutropenia.

First, if a patient develops severe neutropenia on venetoclax, is your first response typically to withhold venetoclax, to dose reduce venetoclax, or to continue venetoclax with G-CSF support given concomitantly?

Second, any thoughts on the use of fungal prophylaxis while on BTK inhibitor therapies, empirically versus during concomitant steroids, neutropenia, etc?

And third, do you withhold targeted agents in CLL patients who develop febrile neutropenia while on those targeted agents?

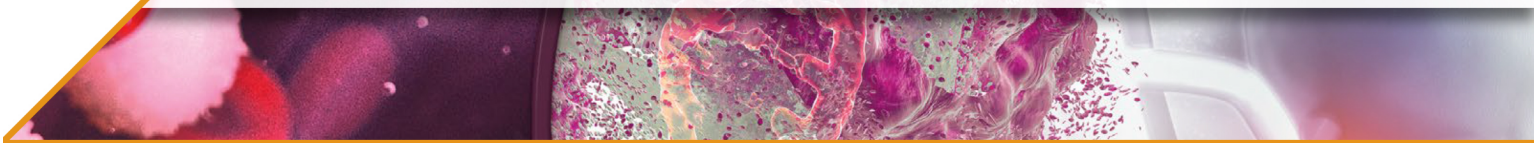
Let's start with a basic review of tumor lysis syndrome. We know that this is an oncologic emergency due to the rapid release of intracellular contents of tumor cells. This can occur either spontaneously prior to starting treatment or, more commonly, in the setting of an active treatment against that cancer.

From an electrolyte perspective, the disorder is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. When we see these electrolyte abnormalities in the absence of clinical sequelae, we refer to this as laboratory TLS.

However, these electrolyte imbalances may become severe enough to cause acute renal failure, cardiac arrhythmias, seizure, loss of muscle control, and even death, and any of these clinical sequelae would be referred to as clinical TLS.

Identifying at-risk patients is essential to prevent life-threatening complications, treatment delays, and permanent renal insufficiency or failure that can be due to TLS.

So what are the features of TLS for which prophylaxis should be considered? Particularly in patients with CLL, those who are receiving treatment with venetoclax and/or obinutuzumab are at higher risk and need to be monitored closely.



Other factors associated with an increased risk of TLS in patients with CLL include bulky lymph node disease; elevated white blood cell count, particularly an absolute lymphocyte count of greater than 25,000; renal insufficiency; those patients already with spontaneous TLS prior to starting treatment; those patients with progressive disease after small-molecule inhibitor therapy…most commonly, these are patients who are experiencing disease progression while on ibrutinib; and patients with pre-existing elevated uric acid.

We know that TLS can occur in patients with CLL who are treated with various targeted agents, again, particularly in the setting of venetoclax and obinutuzumab. We also know that careful risk stratification and prophylaxis strategies can effectively mitigate TLS risk. If TLS occurs, aggressive management is warranted, and this can include hospitalization in some cases.

We know now from our experience clinically with venetoclax and CLL, that if we follow this guidance, which is outlined in detail in the label for venetoclax, that the drug can be delivered safely, and it's a highly efficacious novel therapy for CLL.

Now let's dive a little bit more deeply into venetoclax. We know that venetoclax is a highly potent and orally bioavailable Bcl-2 specific inhibitor targeting the mitochondria of the cells. This drug is so potent that early in the drug's development, unfortunately, there were two deaths due to TLS that were reported in CLL patients treated with venetoclax. These deaths occurred in patients who were treated with venetoclax in a manner different from the eventual approval, because after these deaths on the study, the program was revised to mitigate the risk for TLS, and venetoclax is now dosed on a ramp-up schedule, along with a TLS risk-stratification scheme that includes prophylaxis and careful monitoring for TLS.

One of the key factors that we need to consider as we're thinking about starting venetoclax in a patient with CLL is their overall risk for developing TLS, and this is really a continuum based on multiple factors. First, we need to assess the risk factors for TLS. These include tumor burden, renal function, and other comorbidities. Starting at the top, we can see that tumor burden is characterized by the size of the largest lymph node conglomerate and the height of the absolute lymphocyte count.

Expert Answers to Common Questions for Who's at Risk?

Preventing and Managing Tumor Lysis Syndrome and Neutropenia in CLL

Patients are at low risk for TLS if they have all lymph nodes less than 5 cm and an absolute lymphocyte count less than 25. Medium risk includes any lymph node or lymph node conglomerate between 5 and 10 cm or an absolute lymphocyte count that's greater than 25. And patients at high risk for TLS include those patients with any lymph node conglomerate that's 10 cm or greater or if they have both a lymph node conglomerate greater than 5 cm and an absolute lymphocyte count greater than 25.

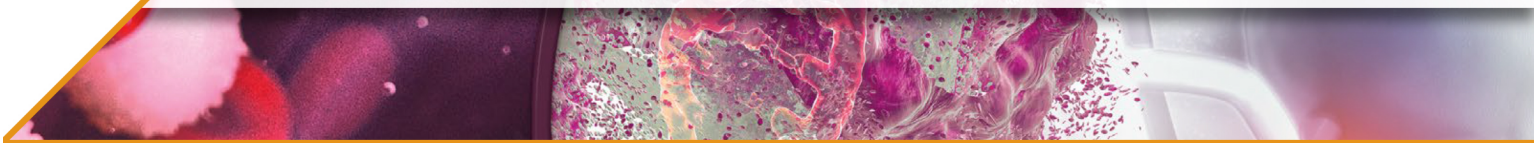
Renal function also plays an important role here. Those patients with a creatinine clearance of less than 80 are at increased risk for TLS. And given that CLL is most commonly a disease of the elderly, many, if not most of our patients, already have a creatinine clearance less than 80.

Other comorbidities that may contribute to TLS risk include splenomegaly, abnormal baseline blood chemistry laboratory results, dehydration, and inability to tolerate oral hydration.

So we've put all these factors together, and it can help us to establish the risk for TLS in an individual patient. I like to think of this as a patient being either at risk or at greater risk because this implies that all patients have at least some risk for TLS, which is true, but that there are some patients at greater risk who we need to be particularly mindful to prophylax and monitor carefully for TLS.

Let's talk specifically about the venetoclax dose initiation and in particular the 5-week dose ramp-up schedule. We start venetoclax in all patients at 20 mg. Although, I'll add that if you have a patient that you're particularly concerned about, you could start even lower at 10 mg. But for most patients, 20 mg is a reasonable starting dose and is what is recommended and labeled for venetoclax.

We give the 20-mg dose for 1 week, and if patients are doing well and have no evidence of TLS, then during week 2, they can ramp up to 50 mg for 1 week. This pattern continues in week 3 at 100 mg, week 4 at 200 mg, and week 5 at 400 mg, which is the eventual dose that most patients can reach. This gradual ramp-up over 5 weeks can gradually reduce the tumor burden and debulk the disease, which thereby decreases the risk for TLS.



In general, we recommend that patients continue on venetoclax 400 mg daily after the ramp-up because this is where we have the most robust long-term data for venetoclax from clinical trials and where we can be confident that patients will likely enjoy a long progression-free survival, as was observed in those trials. The long-term efficacy of lower doses is less certain, but from the Phase 1 study of venetoclax, we do have a hint that possibly patients who are treated with lower dose venetoclax over longer periods of time may have a shorter progression-free survival than those patients who are treated at 400 mg or higher.

We do have to be mindful that concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during the ramp-up is contraindicated in patients with CLL and small lymphocytic leukemia because this can increase the exposure to venetoclax and thereby increase the risk for TLS. This can be particularly useful to keep in mind with particular antibiotics and especially antifungal medicines, such as the azoles, which can interact with venetoclax and increase the exposure of the drug.

Let's talk in more detail about TLS prophylaxis and monitoring measures that we can use to reduce the risks for TLS with venetoclax. The pillars of this approach include hydration, anti-hyperuricemic agents, laboratory monitoring, and, in some cases, hospitalization. For most patients, this begins with oral hydration. The recommendation is about 1.5 to 2 liters starting 2 to 3 days before the first dose of venetoclax. For higher-risk patients, we also use intravenous fluids on the day of venetoclax administration, and in patients who are hospitalized, during the hospitalization, and the rates can range from about 150 to 200 cc per hour of normal saline.

With regard to anti-hyperuricemic agents, all patients should receive some form of anti-hyperuricemic therapy 2 to 3 days prior to the first dose. For most patients this can be allopurinol, usually dosed at 300 mg daily in patients with normal renal function but can be dose-reduced in patients with abnormal renal function. In patients who have allopurinol allergies, febuxostat can be considered as a good alternative. In patients who have a baseline elevated uric acid or a very high tumor burden and are at high risk for TLS, one can consider rasburicase as a prophylactic measure.

With regard to laboratory monitoring, we always need to check the labs pre-dose to have a good baseline prior to starting venetoclax. For the low-to-medium risk patients, we then like to check about 6 to 8 hours after that initial dose at each

different dose level during the dose ramp-up. Particularly for patients at the 20 and 50 mg levels and even in subsequent weeks for other patients, it's also helpful to check 24 hours after that new dose to look for any evidence of late TLS.

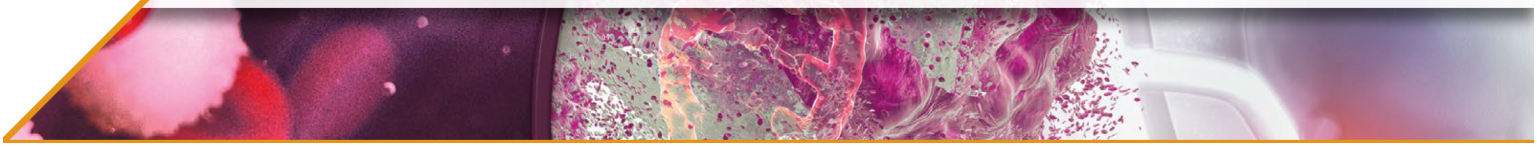
Now for patients with high-risk disease, we would consider generally hospitalizing such patients, particularly if their creatinine clearance is less than 80. In inpatients, it's useful to get the laboratories a little more frequently, usually at pre-dose, 4, 8, 12, and 24 hours after each new dose level. For some of our patients who have difficulty with being stuck for blood draws, we sometimes will place a PICC line to facilitate the ease of these blood draws.

If we are going to try to treat higher-risk patients in the outpatient setting, we can still do the pre-dose 6 to 8 hour and 24-hour labs at subsequent dose ramp-ups, but we need to monitor these patients very closely and be prepared to hospitalize them should we start to see any changes in their electrolytes.

With regard to hospitalization specifically, this is really based on the physician's assessment. Some patients may need to be hospitalized after the first dose of venetoclax for more intensive prophylaxis and monitoring if any electrolyte changes are observed during that first 24-hour period.

So, in terms of summarizing some of the key monitoring measures for venetoclax TLS prophylaxis, these include trying to anticipate TLS, knowing which patients are at higher risk through these risk-assessment tools, and being careful to premedicate patients with anti-hyperuricemic therapy and ensuring adequate hydration both orally and, if necessary, intravenously. Blood chemistries need to be monitored closely, and electrolyte abnormalities need to be managed promptly. This does require that laboratories need to be resulted quickly and the clinician in charge of the patient contacted so that they can quickly make a decision about how to proceed.

We need to be prepared to interrupt venetoclax dosing, if needed. For most patients with CLL, this is not an issue because it is a chronic disease, and it's generally safe to interrupt therapy. One exception to this can be patients who have disease progression on drugs like ibrutinib, who may have much more aggressive CLL that can flare at lower doses, and we need to be a little more careful to interrupt dosing there and only really do it if needed.



In terms of TLS prophylaxis and monitoring, we do need to employ more intensive measures as the overall risk increases, including intravenous hydration, more frequent monitoring of labs, and in some cases, hospitalization.

So again, venetoclax initiation, on day 1, we encourage the patients to stay well-hydrated and to take their venetoclax early in the morning. This can be done with trustworthy patients at home, as long as they're coming into the center later that morning for their initial lab draw. We recommend that they take venetoclax with food and water to help with absorption. Labs can then be drawn 6 to 8 hours after that first dose and need to be analyzed promptly, and electrolytes need to be managed promptly, as well.

On day 2, the patients return 24 hours after their first dose for a laboratory evaluation. And again, electrolytes need to be managed promptly. An important point is that the second dose of venetoclax, that day-2 dose, should only be taken after a 24-hour blood chemistry result has been evaluated and any abnormalities corrected. The second dose can be taken at home if instructed by the prescribing physician with a trustworthy patient, and again encouraging patients to take their venetoclax with food and water, leading to more predictable absorption.

On days 3 through 7 of each week, the patient will take subsequent daily doses at approximately the same time each day with food and water, but generally no additional laboratory evaluations are needed during days 3 through 7.

The patient then returns on day 8 for their next dose ramp-up and has additional laboratory evaluation at that time.

We also like to remind patients that there are certain fruits that they need to avoid, such as grapefruit products, Seville oranges, and starfruits.

By implementing this venetoclax dose ramp-up scheme, we have shown that this significantly mitigates the risk for TLS. Using this 5-week venetoclax dose ramp-up and the TLS prophylaxis and monitoring measures that we just reviewed, TLS has been infrequent in larger series.

I published a study, in collaboration with a number of other investigators, looking across the early-phase venetoclax monotherapy program in CLL, where we looked at 350 patients treated with venetoclax. And of the patients treated with

the 5-week dose ramp-up that's now approved, there was only a 1.4% chance of laboratory TLS, and there were no cases of clinical TLS in that series.

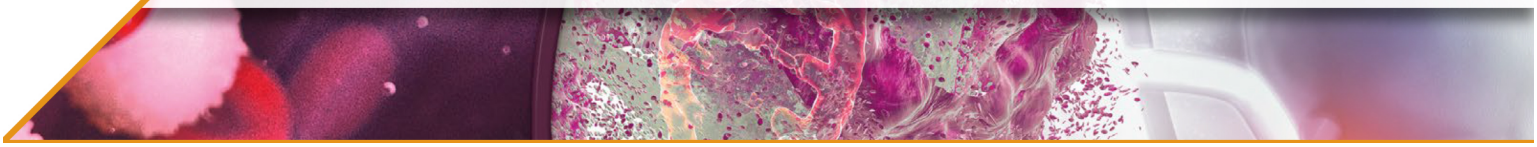
Roeker and colleagues, a couple of years ago, reported on a series of patients treated in the real-world setting, nearly 300 patients, and in that setting, they did see 2.7% of patients with clinical TLS and 5.7% of patients with laboratory TLS, perhaps reflecting more of the increased comorbidity burden of patients treated outside of the clinical trial setting. So this does highlight that in your clinical practice, you are likely to see some TLS if you use enough venetoclax, and so you do need to be prepared to treat it aggressively, if needed, even though most patients will do well without showing signs of TLS.

So with regard to prophylaxis, TLS is best managed if anticipated and treatment is started prior to therapy. Again summarizing, this could include aggressive hydration, certainly oral but possibly also intravenous; management of hyperuricemia, certainly with drugs like allopurinol but also with rasburicase when needed; frequent electrolyte monitoring; proactive correction of any electrolyte abnormalities; and again, emphasizing the importance of uric acid-lowering therapies such as allopurinol, febuxostat for patients who may have allopurinol allergies, and rasburicase when needed.

Treatment for established TLS is also mentioned specifically in the NCCN Guidelines. They also emphasize that TLS is best managed if anticipated and treatment is started prior to chemotherapy or venetoclax-based therapy. They again highlight the centerpieces of treatment that include rigorous hydration, management of hyperuricemia, and frequent monitoring of electrolytes and aggressive correction, which is really essential.

They highlight some of the potential risks if these measures are not followed, including acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.

They also agree with the recommendation for first-line therapy with allopurinol or febuxostat 2 to 3 days prior to starting treatment and continuing for at least a couple of weeks. And actually, I would highlight that in the case of venetoclax, I like to continue allopurinol therapy throughout the 5-week ramp-up period and only discontinue it once they're solidly on their final dose of 400 mg daily.



NCCN Guidelines also highlight rasburicase as an option for patients with any of the following risk factors: Urgent need to initiate therapy in a high tumor bulk patient; situations where adequate hydration may be difficult or impossible, for example, in patients with significant heart failure where you may be worried about the volume overload; as well as the patients with acute renal failure.

Let's talk in a little more detail now about rasburicase. As you know, this is a recombinant urate oxidase that converts uric acid to allantoin, which can then easily be excreted by the kidneys. Rasburicase lowers already high levels of uric acid in addition to preventing further hyperuricemia. The drug has been approved by the FDA for the initial management of plasma uric acid levels in both pediatric and adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid.

As a reminder, there's a boxed warning on rasburicase around hypersensitivity reactions, hemolysis, methemoglobinemia in patients with G6PD deficiency, and you have to be mindful that it's also a drug that can interfere with uric acid measurements. And once rasburicase is given, you need to make sure that the sample is sent chilled on ice and sent to the lab for quick evaluation.

Because of the risk of methemoglobinemia, we do generally recommend G6PD levels should be tested prior to initial administration.

The FDA approved rasburicase based on a weight-based measurement. But subsequent studies actually showed that rasburicase can be safely and very effectively given at a fixed dose, which tends to be a lower dose, at 6 mg or 3 mg flat dose, and this has comparable efficacy to the higher-weight-based dosing.

Because this is such an expensive medication, it is helpful to use these lower doses to keep costs down, and in general, to be mindful of the expense of this drug, and use it only when clinically indicated.

There have been some phase 3 studies including rasburicase, including one that showed a significant protection from TLS-related hyperuricemia as compared with allopurinol alone. The response rate for rasburicase on its own is about 87%, in this study, compared to 66% with allopurinol alone. The plasma uric acid response rate in the patients at high-risk TLS, similarly, was 89% with rasburicase versus 68% with allopurinol. Similarly, in patients with baseline

hyperuricemia, the plasma uric acid response rate was 90% with rasburicase and 53% with allopurinol.

One of the most remarkable things about rasburicase is just how quickly it works. The average time on this study was 4 hours of time from plasma uric acid control in these patients with hyperuricemia, whereas it was 27 hours in patients who were treated with allopurinol.

So to summarize,

Do you want to withhold venetoclax during TLS treatment, and when do you restart, and what dose?

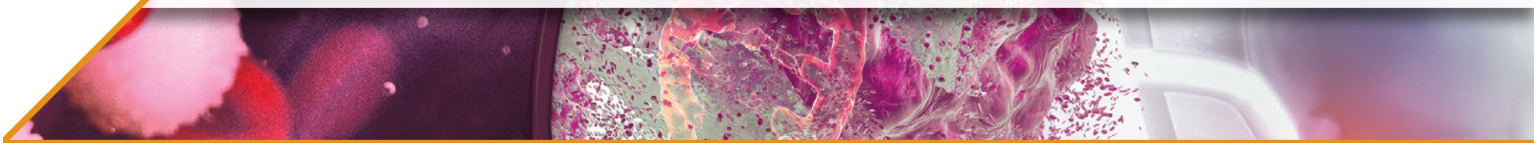
So I would say, generally, you should withhold venetoclax if you're seeing evidence of TLS, even if it's laboratory TLS, and look to see that the electrolytes are beginning to resolve and hopefully returning to normal before resuming venetoclax. As I mentioned, in most CLL patients, we have time, this is a chronic disease, we don't need to rush into higher doses of venetoclax, with the occasional exception of disease progression on a drug like ibrutinib, which may need a little bit more aggressive intervention.

Generally, when I do restart, I like to restart at the same dose where I left off, or if it's a short hold and the electrolytes resolve quickly, I can move up to the next dose level if they're still in the dose ramp-up period.

Sometimes there can be a more sluggish change in measures such as LDH. So for example, in a patient who has electrolyte abnormalities consistent with laboratory TLS and a marked elevation in LDH, I wait until the electrolyte abnormalities normalize. But the LDH may take several days to normalize, and as long as it's convincingly trending down, I don't necessarily wait for the LDH to normalize before resuming venetoclax therapy.

Do you have to ramp up the venetoclax dose to 400 mg if the patient has an excellent response to a lower dose?

I do try to get up to 400 mg if the patient is tolerating the drug well, because again, we have the longest-term data with long-term therapy with 400 mg of venetoclax and a suggestion from the phase 1 study that the progression-free survival may be longer in those patients who tolerate the higher dose of 400 mg.



That being said, if a patient's running into issues with continued toxicities, whether it's GI toxicities or neutropenia, I do sometimes need to leave patients on a lower dose of 200 or 300 mg, for example, and that can still be an effective dose, but only if patients are having tolerability issues.

When do you feel safe to discharge patients during venetoclax ramp-up?

These patients get admitted at our center the night before to get intravenous hydration overnight and so that they can start early in the morning with their venetoclax dose. They get laboratory monitoring throughout the day, and then stay one more night, and 24 hours later, if the electrolytes look good 24 hours after that venetoclax dose, that's generally when I will discharge the patients home.

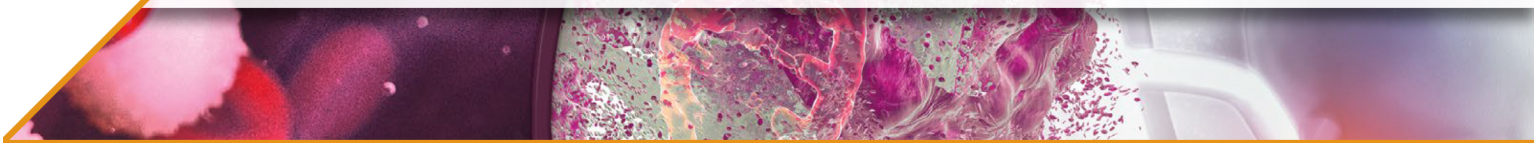
However, if we've seen laboratory changes of TLS, particularly at that 24-hour mark, then I will continue to monitor the patient in the hospital for as long as it takes for those electrolyte changes to convincingly resolve. And again, with the LDH, it does not need to resolve but should at least be solidly trending down before I will discharge the patient.

Question on a high-risk TLS patient: Would you readmit for a second dose of venetoclax ramp-up to 50 mg?

Definitely yes, that would be actually recommended by the label of venetoclax. Basically, for all the patients who are being admitted for high-risk disease, you would want to admit for the 20-mg and the 50-mg ramp-up 1 week later. After that, if the patient's doing well, even if they started as high-risk, hopefully their absolute lymphocyte count is beginning to trend down, and their lymph nodes are shrinking. And so those patients who are initially high-risk can potentially be treated safely in the outpatient setting for the subsequent ramp-up doses to 100, 200, and 400 mg.

Question on can rasburicase be given in the outpatient setting prophylactically?

This can vary from center to center. At our center, we do give rasburicase in the outpatient setting. This can be a way to potentially prevent hospitalization in a patient with high baseline uric acid who may be at high risk for TLS. And so we find this to be very useful.



With regard to the questions on neutropenia:

If a patient develops severe neutropenia on venetoclax, is your first response typically to withhold venetoclax, to dose reduce venetoclax, or to continue venetoclax with G-CSF support?

Here, I try to usually use the latter approach of continuing venetoclax while providing concomitant G-CSF support, particularly if I use a longer-acting G-CSF like pegfilgrastim, I find that most patients are able to continue with their venetoclax without the need to withhold or dose reduce, as long as you give the pegfilgrastim and monitor the neutrophil count closely.

And in general, patients, despite having relatively high rates of neutropenia with venetoclax, have a relatively low rate of infection…does not seem to be any higher than other therapies with CLL.

For patients who have neutropenia, despite G-CSF support while on venetoclax, that's when I would typically briefly hold the drug and then dose-reduce when I resume the drug.

A question on thoughts on the use of fungal prophylaxis while on BTK inhibitor therapy specifically, whether empirically during concomitant steroids, neutropenia, or other risk factors.

So in general, I would say that either with BTK inhibitors or with venetoclax, I do not use empiric antifungal prophylaxis, again, because the risks of infection with these targeted therapies tend to be lower than what we expect from neutropenia with chemoimmunotherapy. Even in patients with long-term need for steroids, I would not necessarily use antifungal prophylaxis, although if you broadly define that to include *Pneumocytis jiroveci* pneumonia (PJP), then in that case, yes, I would.

Those patients on longer-term, concomitant steroids should certainly be on PJP prophylaxis with trimethoprim/sulfamethoxazole or equivalent. And those patients who are at particularly high risk, based on prior infections, could be considered for antifungal prophylaxis, if they've had a prior fungal infection, but otherwise, that is generally not necessary. And also you have to be mindful of the drug-drug interactions, as I mentioned with the azoles. So I try to avoid those when I can.

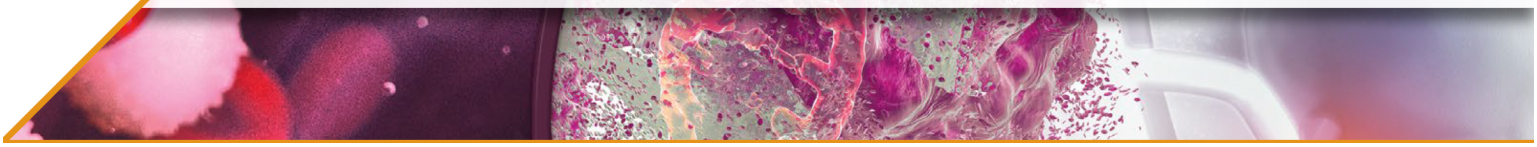
And a final question is around do you withhold targeted agents in CLL patients who develop febrile neutropenia?

So generally, my answer to that question is yes, although it depends a little bit on where the patients are within the course of their therapy. If this is a patient who just recently started on their novel agent, and their CLL is at a high-disease burden, and they're otherwise looking very well clinically, I may continue for a brief time to see how they do.

But I would say for the majority of patients who develop febrile neutropenia while on targeted agents, it is prudent to withhold the targeted agent for a brief time. Usually, this might be just a few days, if the patient's hospitalized and receiving IV antibiotics. And then typically when the patient is converted to oral antibiotics, and particularly once they go home without fever, that is a good time to resume the novel agent.

Particularly again, for patients earlier in their course, I try not to withhold for more than a few days because you do risk the CLL progressing during that time. But for patients who have been on targeted agents for a long time, several months or particularly several years, there I might feel much more comfortable with a longer withhold of the targeted agent to allow for more complete resolution of the infection.

So with that, I would like to thank you very much for your attention and thank you for participating in this activity.



References

Cairo MS, Thompson S, Stern L, Sherman S. Incidence of treatment-related, laboratory and clinical tumor lysis syndrome. *Blood* 2012;120(21):238.

Cortes J, Moore JO, Maziarz RT, et al. Control of plasma uric acid in adults at risk for tumor Lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone—results of a multicenter phase III study. *J Clin Oncol*. 2010;28:4207.

Davids MS, Hallek M, Wierda W, et al. Comprehensive safety analysis of venetoclax monotherapy for patients with relapsed/refractory chronic lymphocytic leukemia. *Clin Cancer Res*. 2018;24:4371-4379.

Dinnel J, Moore BL, Skiver BM, Bose P. Rasburicase in the management of tumor lysis: an evidence-based review of its place in therapy. *Core Evid.* 2015;10:23-38.

Elitek (rasburicase) [prescribing information]. July 2016. Bridgewater, New Jersey: sanofi-aventis. http://products.sanofi.us/elitek/elitek.pdf.

Maloney K, Denno M. Tumor lysis syndrome: prevention and detection to enhance patient safety. *Clin J Oncol Nurs*. 2011;15:601-603.

Roberts AW, Ma S, Kipps TJ, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374:311-322.

Roeker LE, Fox CP, Eyre TA, et al. Tumor lysis, adverse events, and dose adjustments in 297 venetoclax treated CLL in routine clinical practice. *Am Assoc Cancer Res*. 2019;25:4264-4270.

Seymour JF, Ma S, Brander DM, et al. Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b study. *Lancet Oncol*. 2017;18:230-240.

Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. *Lancet Oncol.* 2016;17:768-778.

Venclexta (venetoclax) [prescribing information]. May 2020. South San Francisco, California: Genentech, Inc. http://www.rxabbvie.com/pdf/venclexta.pdf.

Venclexta (venetoclax). 2020. Risk assessment, prophylaxis, and monitoring measures for TLS. https://www.venclextahcp.com/cll/dosing/risk-assessment.html.

Wierda WG, Byrd JC, Abramson JS, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 1.2022. © 2021 National Comprehensive Cancer Network, Inc. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.