

Advanced Practice Perspectives on Preventing and Managing Tumor Lysis Syndrome and Neutropenia in Chronic Lymphocytic Leukemia

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Abstract

Tumor lysis syndrome (TLS) and neutropenia are significant toxicities in the treatment of chronic lymphocytic leukemia (CLL). Both TLS and neutropenia can lead to potentially life-threatening complications for patients with chronic lymphocytic leukemia undergoing antineoplastic therapy. This article focuses on diligent risk assessment, prophylaxis, early identification, monitoring, patient education, and prompt intervention for TLS and neutropenia. These are all necessary steps to reduce life-threatening complications. Guidelines are available for risk assessments for both TLS and neutropenia. Once risk is established, prophylaxis and monitoring recommendations can be found in available guidelines. There are no established guidelines or widely used decision-making standards for the treatment of clinical TLS. General management strategies are well documented in the literature, with some degree of customization to each individual patient. If fever occurs in the setting of neutropenia, there are well-established guidelines for management, including guidance on anti-infective agents and use of growth factors. In addition, awareness and proper actions regarding TLS and neutropenia are key to preventing treatment delays, dose reductions, or treatment discontinuation. Adequate planning for TLS and neutropenia is critical to optimize patient outcomes.

Tumor lysis syndrome (TLS) is an oncologic emergency caused by the rapid release of intracellular contents of tumor cells into the peripheral blood, although it may also occur spontaneously.

Laboratory TLS is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. In laboratory TLS, electrolyte imbalances are not severe and do not cause systemic sequelae. Clinical TLS occurs when elec-

trolyte imbalances become severe and lead to acute renal failure, cardiac arrhythmias, seizures, loss of muscle control, and even death. Assessing risk for each patient is critical to preventing life-threatening complications (Cairo, Thompson, Stern, & Sherman, 2012; National Comprehensive Cancer Network [NCCN], 2020a; Wilson & Berns, 2014).

TUMOR LYSIS SYNDROME: IDENTIFYING AT-RISK PATIENTS, PREVENTION, AND MANAGEMENT

Risk assessment for TLS is based on the patient's diagnosis, with hematologic malignancies carrying the highest risk; other risks include planned treatment regimen and renal function, with renal insufficiency further increasing a patient's risk level (Howard, Jones, & Pui, 2011; Mughal, Ejaz, Foringer, & Coiffier, 2010). Risk assessment allows categorization into one of three groups: low risk, intermediate risk, or high risk. Low-risk patients have less than a 1% risk of developing TLS. Intermediate-risk patients have 1% to 5% risk of developing TLS, and high-risk patients have a greater than 5% risk of developing TLS (Cairo, Coiffier, Reiter, & Younes, 2010; Mackiewicz, 2012). The current grading and classification systems for clinical and/or laboratory TLS include the National Cancer Institute's Common Terminology Criteria for Adverse Events, the Cairo-Bishop classification system, and the modified Cairo-Bishop system (Cairo & Bishop, 2004; Howard et al., 2011; National Cancer Institute, 2017).

A TLS Expert Panel published recommendations on TLS risk assessment in adults and children with malignant disease (Cairo et al., 2010). These recommendations assign risk based on malignant disease type, biological signs of TLS, and renal dysfunction or renal involvement. Per Cairo and colleagues (2010), chronic lymphocytic leukemia (CLL) is a low-risk disease (LRD) when being treated with anthracycline therapy only and intermediate-risk disease (IRD) when being treated with biological and/or targeted agents. Once disease risk is established, recommendations include further stratification based on renal function. For CLL patients with LRD, normal renal function assigns them as low risk (LR) for TLS, while the pres-

ence of renal dysfunction or renal involvement elevates their TLS risk to intermediate risk (IR). For CLL patients with IRD, normal renal function with normal serum uric acid, phosphate, or potassium level assigns them as IR for TLS. For IRD CLL, renal dysfunction, renal involvement, or normal renal function with abnormal serum uric acid, phosphate, or potassium level elevates their TLS risk to high risk (HR) for TLS (Cairo et al., 2010).

As reflected in recommendations by Cairo and colleagues (2010), patients with CLL have not been historically considered high risk for TLS; however, because of the rapid responses seen with newer novel agents, particularly oral small molecule inhibitors, TLS is now a common consideration when treating patients with CLL (NCCN, 2020a). Risk factors for TLS in patients with CLL include high absolute lymphocyte counts ($> 25 \times 10^9/L$), bulky lymphadenopathy, preexisting renal insufficiency, and concurrent use of nephrotoxic agents. In addition, in CLL, targeted and/or biologic therapies carry a higher risk for TLS than chemotherapy alone (NCCN, 2020a).

Prophylactic Measures

Tumor lysis syndrome prophylaxis should be considered for patients with CLL with risk factors mentioned previously and for those receiving venetoclax, chemoimmunotherapy, lenalidomide, and/or obinutuzumab; and for spontaneous TLS, progressive disease after small-molecule inhibitor therapy, and preexisting hyperuricemia (NCCN, 2020a).

Once risk assessment has been completed, TLS is best managed with prophylactic measures before antineoplastic therapy (NCCN, 2020a). Management can include aggressive hydration, management of hyperuricemia, frequent electrolyte monitoring, prompt correction of any electrolyte imbalances, and antiuricemics. Commonly used anti-uricemics include allopurinol, febuxostat, and rasburicase (NCCN, 2020a; Wilson & Berns, 2014). Prophylactic strategies range from outpatient management with oral hydration and oral antiuricemics to inpatient management with intravenous hydration and antiuricemics. There are four critical considerations when assessing a patient for prophylactic measures: medications, hydration, diuretics, and hemodialysis.

Allopurinol is a xanthine oxidase inhibitor that decreases the generation of uric acid; however, it may not reduce existing uric acid (Wilson & Berns, 2014). Typical dosing is 300 mg orally daily, although up to 600 mg may be used, with renal dosing, as appropriate (Casper Pharma LLC, 2018). Treatment with allopurinol should start 2 to 3 days before antineoplastic therapy and is continued daily for a minimum of 7 days. It is most useful in prophylaxis and may be less useful in the treatment of TLS (Cairo et al., 2010; Wilson & Berns, 2014). Common side effects include skin rash, renal insufficiency, hepatic toxicity, nausea, vomiting, and drowsiness. Allopurinol should be discontinued immediately if a skin rash or other signs indicating an allergic reaction occurs because Stevens-Johnson syndrome has been reported (Cairo et al., 2010; Casper Pharma LLC, 2018).

Febuxostat is also a xanthine oxidase inhibitor that prevents the formation of uric acid and is dosed at 120 mg daily (Takeda Pharmaceuticals America, Inc., 2019). In the setting of TLS, it is used for patients with allopurinol intolerance or those in whom allopurinol is not advisable (Wilson & Berns, 2014). Febuxostat is also ideally started 2 to 3 days before antineoplastic therapy and is continued for a minimum of 7 days. In a phase III study of allopurinol vs. febuxostat that randomized 346 patients at intermediate to high risk for TLS, patients treated with febuxostat achieved significantly superior uric acid control, with comparable side effect profiles and renal function preservation between the two arms. Febuxostat is U.S. Food & Drug Association (FDA) approved for use in the chronic management of hyperuricemia in patients with gout and is not recommended for the treatment of asymptomatic hyperuricemia.

Boxed warnings include gout flare, cardiovascular thrombotic events (myocardial infarction and stroke), and hepatic failure (Spina et al., 2015; Takeda Pharmaceuticals America, Inc., 2019).

Rasburicase is recombinant urate oxidase that converts allopurinol to allantoin, which is water soluble and easily excreted by the kidneys (Maloney & Denno, 2011). Rasburicase lowers uric acid levels in addition to preventing further uric acid formation (Dinnel et al., 2015). It is administered IV over 30 minutes daily, as needed, at a dose of 0.2 mg/kg, starting at least 4 hours before antineoplastic therapy (Sanofi-aventis US, LLC, 2019). Boxed warnings include hypersensitivity reactions, hemolysis, methemoglobinemia, and interference with uric acid measurements. In a phase III study of rasburicase vs. rasburicase + allopurinol vs. allopurinol, 280 patients at high risk for TLS were enrolled (Cortes et al., 2010). Rasburicase was superior to rasburicase + allopurinol and allopurinol monotherapy, with response rates of 87%, 78%, and 66%, respectively. In addition, response rates in patients at high risk along with baseline hyperuricemia were superior in the rasburicase arm vs. allopurinol monotherapy at rates of 89% and 68%, and 90% and 53%, respectively. Time to uric acid control in hyperuricemic patients was 4 hours in both the rasburicase and rasburicase + allopurinol arms and 27 hours in the allopurinol monotherapy arm (Table 1).

Based on these results, rasburicase is FDA approved for the initial management of plasma uric acid levels in pediatric and adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy expected to result in TLS and subsequent elevation of plasma uric acid. Black box warnings include hypersensitivity reactions, hemolysis, methemo-

Table 1. Summary of Efficacy: Controlling Plasma Uric Acid

	Rasburicase	Rasburicase + allopurinol	Allopurinol
Response rate (% of patients with plasma uric acid levels ≤ 7.5 mg/dL between days 3 and 7)	87%	78%	66%
Plasma uric acid response rate: patients at high risk for TLS	89%	-	68%
Plasma uric acid response rate: patients with baseline hyperuricemia	90%	-	53%
Time to plasma uric acid control for hyperuricemic patients	4 hr	4 hr	27 hr

Note. Information from Cortes et al. (2010); Dinnel et al. (2015); Maloney & Denno (2011); Sanofi-aventis US, LLC. (2019).

globinemia, and interference with uric acid measurements (Sanofi-aventis US, LLC, 2019). Dosage is weight based, but other options are fixed doses of 3 mg or 6 mg with comparable efficacy (Sanofi-aventis US, LLC, 2019). Despite the effectiveness of rasburicase, it should be used only when truly clinically indicated due to its high cost (Dinnel et al., 2015).

Hydration for patients at low risk for TLS is often achieved with aggressive oral hydration. For patients at high risk for TLS, IV hydration, typically with normal saline, should be administered at a rate of 2,500 to 3,000 mL/m²/day, although individual patient tolerance and comorbidities must be taken into consideration (Tosi et al., 2008; Will & Tholouli, 2011). Hydration should be administered to maintain urine output at 2 mL/kg/hr or at least 100 mL/hr (Howard et al., 2011; NCCN, 2020a).

Diuretics are a supportive care measure and should only be used after adequate hydration has been achieved. Diuretics are used to help prevent or treat fluid overload but do not affect outcomes or the need for hemodialysis (Mughal et al., 2010). In patients undergoing imaging with contrast, concurrent use of diuretics may increase the risk of contrast-induced nephropathy. Furosemide may contribute to uric acid nephropathy through increased uric acid or calcium precipitate formation in the renal tubules. This risk is low in the setting of concurrent aggressive IV hydration; however, diuretics should be used sparingly unless clinically relevant volume overload is noted (Howard et al., 2011; Wilson & Berns, 2014).

Finally, given the older age and reduced baseline renal function of the average CLL patient, hemodialysis considerations may be appropriate based on overall TLS risk. Hemodialysis may be used in clinical TLS, in the setting of severe hyperkalemia, acidosis, hypervolemia unresponsive to diuretics, or severe uremic symptoms such as pericarditis or encephalopathy (Givens & Crandall, 2010). There are currently no criteria or guidelines for when to initiate hemodialysis. It is generally recommended that patients with extremely high phosphorous levels receive ongoing renal substitution therapies, such as continuous veno-venous hemofiltration (Mughal et al., 2010).

Case Study 1

Mr. L is a 62-year-old male with CLL scheduled to receive second-line therapy with bendamustine and rituximab after progression on ibrutinib. Indications for treatment include recent increasing fatigue, symptomatic splenomegaly with abdominal fullness and early satiety, 4 cm bilateral axillary nodes and numerous 2 to 3 cm nodes in the retroperitoneum and bilateral inguinal regions on imaging, white blood cells (WBC) $105,000 \times 10^9/L$ (90% lymphocytes) and platelets $89,000 \times 10^9/L$. He had normal serum creatinine, electrolytes, and uric acid. Comorbidities included well-controlled hypertension and hypercholesterolemia.

The risk assessment is notable for high-risk features of a diagnosis of CLL, high lymphocyte count, extensive lymphadenopathy, splenomegaly, progression on small molecule inhibitor therapy, and planned chemoimmunotherapy, per NCCN Guidelines (2020a). He has favorable findings of normal serum creatinine, phosphate, potassium, and uric acid. In the absence of TLS prophylaxis guidelines, his oncology team deems him as intermediate risk for TLS. Mr. L requires TLS prophylaxis with aggressive oral hydration and allopurinol, and will initiate treatment in the outpatient setting. Patient education is also important to ensure Mr. L understands the rationale for and importance of TLS prophylaxis measures and appropriate reporting to his health-care team. He will have baseline TLS labs drawn, including uric acid, potassium, phosphorous, and calcium, and will have them repeated on days 2 and 3 of cycle 1. Aggressive management of any laboratory abnormalities is appropriate to minimize his risk of progressing to clinical TLS.

Spotlight: Patient Education and Adherence to Prophylaxis

Patient education is important for early recognition of any symptoms of TLS at home, and is a key part of the successful prophylaxis and management of TLS (Maloney & Denno, 2011). Education about prophylactic drug dosing and schedule, adequate hydration, as well as common and reportable side effects are critical to the prevention of TLS and related complications. In the outpatient setting, patients should also limit foods,

beverages, and supplements high in potassium, phosphorous, and calcium. It is also important to assess adherence to medication schedules and concomitant medications on an ongoing basis (Howard et al., 2011).

Clinical Presentation and Symptoms of TLS

If TLS prevention is unsuccessful, a variety of symptoms may ensue based on the number of tumor cells being lysed and subsequent electrolyte abnormalities (NCCN, 2020a). Common or serious symptoms include nausea and vomiting, shortness of breath, irregular heartbeat, cloudy urine, lethargy, seizures, and joint discomfort. Hallmark laboratory abnormalities include elevated potassium, phosphorous, uric acid, and lactate dehydrogenase levels, with low calcium levels.

Treatment and Monitoring of TLS: Review of Guidelines

Treatment of TLS is focused on rapidly reversing electrolyte abnormalities and minimizing kidney injury (Sarno, 2013). Intervention must be aggressive and timely to prevent the potentially severe consequences of clinical TLS. For patients in the low-risk category, treatment should include oral hydration, IV fluids as needed, allopurinol, and daily laboratory monitoring of uric acid, potassium, phosphorous and calcium with timely review of results (Howard et al., 2011). For intermediate-risk patients, continued oral hydration with IV fluids, allopurinol and/or rasburicase, inpatient monitoring, and laboratory monitoring every 8 to 12 hours are appropriate. For high-risk patients, recommended interventions include oral hydration, IV fluids, allopurinol and rasburicase, cardiac monitoring for arrhythmias, and laboratory monitoring every 6 to 8 hours. In addition, all patients require close monitoring of urine output, volume/fluid status, and daily weights (Mughal et al., 2010).

TLS Assessment in CLL

Part of a TLS risk assessment includes assessment of the intended treatment regimen for CLL. Venetoclax, an oral Bcl-2 inhibitor, has a known risk of fatal TLS (Genentech USA, Inc., 2020; Roeker et al., 2019). In early clinical trials, two deaths from TLS were reported (Genentech USA,

Inc., 2020). Thus, venetoclax is now initiated on a ramp-up schedule (Davids et al., 2018; Genentech USA, Inc., 2020; Roberts et al., 2016; Roeker et al., 2019). Tumor lysis syndrome risk stratification, prophylaxis, and monitoring are also recommended (Table 2). Creatinine clearance < 80 mL/min, splenomegaly, baseline abnormal blood chemistry results, dehydration, or the inability to tolerate oral hydration increase the risk for TLS in patients taking venetoclax (Davids et al., 2018; Genentech USA, Inc., 2020; Roberts et al., 2016; Roeker et al., 2019).

A ramp-up venetoclax dosing schedule is used for all patients with CLL, regardless of tumor burden or TLS risk (Figure 1). Concurrent use of strong or moderate CYP3A inhibitors requires venetoclax dose reduction due to increased risk for TLS (Genentech USA, Inc., 2020).

Tumor lysis syndrome prophylaxis and monitoring are recommended for all patients initiating venetoclax, regardless of risk or tumor burden (Genentech USA, Inc., 2020; Stilgenbauer et al., 2016; Figures 2 and 3).

Although venetoclax monotherapy is continued until disease progression or unacceptable toxicity, newer time-limited regimens of anti-CD20 monoclonal antibodies with venetoclax have become options for the initial treatment of CLL, as well as in the relapsed/refractory setting (Fischer et al., 2019; Seymour et al., 2018). These 1- or 2-year treatment courses give patients alternatives to open-ended treatment options. In the initial therapy setting, obinutuzumab and venetoclax for 1 year is an option. Obinutuzumab is dosed weekly for 3 weeks before venetoclax is initiated and given for 6 months, whereas venetoclax continues for 1 year. Tumor lysis syndrome risk stratification and prophylaxis are undertaken before obinutuzumab dosing and the standard ramp-up of venetoclax is used. To date, the only incidences of clinical TLS with severe abnormalities in uric acid, phosphate, potassium, or calcium resulting in systemic effects have occurred in the obinutuzumab-only phase of treatment before venetoclax initiation.

In the relapsed/refractory setting, rituximab and venetoclax is a 2-year, time-limited option. Again, risk stratification and prophylaxis occur before therapy initiation. In this regimen, the stan-

Table 2. TLS Prophylaxis in Patients Receiving Venetoclax

Tumor burden		Setting
Low	Lymph nodes < 5 cm and absolute lymphocyte counts < $25 \times 10^9/L$	Often treated in the outpatient setting
Medium	Lymph nodes 5 to ≤ 10 cm or absolute lymphocyte count $\geq 25 \times 10^9/L$	Often treated in the outpatient setting
High	Any lymph node ≥ 10 cm or any lymph node > 5 cm and absolute lymphocyte count > $25 \times 10^9/L$	Initiate venetoclax in the inpatient setting

Standard venetoclax ramp-up is followed by rituximab initiation. Rituximab is given for 6 months and venetoclax is continued for 2 years. With venetoclax ramp-up, there have been no cases of clinical TLS (severe electrolyte abnormalities leading to systemic symptoms), although laboratory TLS (nonsevere electrolyte abnormalities without systemic effects) has been noted in approximately 3% of patients (Fischer et al., 2019; Seymour et al., 2018). The incidence of laboratory TLS with venetoclax monotherapy is 1.4% to 5.7%, and the incidence of clinical TLS is 2.7%, with no fatalities since ramp-up dosing was initiated (Davids, et al., 2018; Roberts et al., 2016).

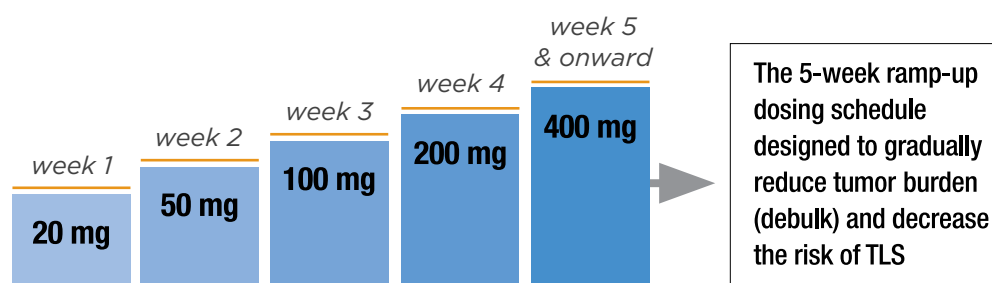
Case Study 2

Ms. O is an 83-year-old female with multiple relapsed CLL starting fourth-line therapy with

venetoclax. Indications for treatment include WBC $189,000 \times 10^9/L$ (82% lymphocytes) and platelets $73,000 \times 10^9/L$. Other remarkable findings include creatinine clearance 45 mL/min, uric acid high normal at 6.0 mg/dL, and up to 5 cm lymph nodes in the abdomen on imaging. Comorbidities include mild osteoarthritis in the bilateral knees and hips, requiring intermittent over-the-counter analgesics.

Risk assessment is remarkable for high lymphocyte count and low creatinine clearance, putting Ms. O at high risk for TLS. Due to her elevated absolute lymphocyte count and renal dysfunction, she meets the criteria for initiating venetoclax during inpatient hospitalization. Inpatient hospitalization allows continuous IV hydration, close monitoring of TLS, and maximum supportive care. Ms. O starts aggressive oral hydration and allopu-

Venetoclax Dose Initiation 5-Week Dose Ramp-up Schedule



- Recommended maintenance dose of venetoclax is 400 mg once daily
- Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated in patients with CLL/SLL due to increased risk of TLS

Figure 1. Venetoclax dose initiation: 5-week dose ramp-up schedule. CLL = chronic lymphocytic leukemia; SLL = small lymphocytic leukemia; TLS = tumor lysis syndrome. Information from EMC (2020); Genentech USA, Inc. (2020).

Venetoclax: TLS Prophylaxis and Monitoring





 HYDRATION	Oral (1.5-2 L); start 2-3 days prior to first dose	IV (150-200 mL/hr) if high risk (high tumor burden)
 ANTI-HYPERURICEMIC AGENTS	All patients should receive anti-hyperuricemic agents 2-3 days prior to first dose If elevated uric acid or high tumor burden, consider rasburicase	
 LABORATORY MONITORING	Pre-dose, 6-8, 24 hours At first dose of 20 mg and 50 mg, and for patients who continue to be at risk Pre-dose at subsequent ramp-up doses	High Risk Consider hospitalization monitoring if CrCL <80 mL/min Inpatient: Pre-dose, 4, 8, 12, and 24 hr Outpatient: Pre-dose, 6-8 hr, 24 hr at subsequent ramp-up doses
 HOSPITALIZATION	Based on physician assessment; some patients may be hospitalized after first dose of venetoclax for more intensive prophylaxis and monitoring during the first 24 hours	

Figure 2. Venetoclax: TLS prophylaxis and monitoring. ALC = absolute lymphocyte count; CrCL = creatinine clearance; LN = lymph node; TLS = tumor lysis syndrome. Information from Genentech USA, Inc. (2020).

Venetoclax Initiation






Day 1	 TAKE VENETOCLAX 0 HOUR <ul style="list-style-type: none"> • Patient may take first dose at home if instructed by prescribing physician • Venetoclax should be taken with food and water 	 DRAW LABS 6-8 HOURS AFTER FIRST DOSE <ul style="list-style-type: none"> • Draw labs 6-8 hours after first dose and analyze results • Manage electrolyte abnormalities promptly
Day 2	 DRAW LABS 24 HOURS AFTER FIRST DOSE <ul style="list-style-type: none"> • Draw labs 24 hours after first dose and analyze results • Manage electrolyte abnormalities promptly 	 TAKE VENETOCLAX Second dose should only be taken after 24-hour blood chemistry results have been evaluated and any abnormalities corrected <ul style="list-style-type: none"> • Patients may take second dose at home if instructed by prescribing physician • Venetoclax should be taken with food and water
Days 3-7	 TAKE VENETOCLAX ONCE DAILY <ul style="list-style-type: none"> • Patient takes subsequent daily doses at approximately the same time each day • Venetoclax should be taken with food and water 	

Figure 3. Venetoclax initiation. Information from Genentech USA, Inc. (2020).

rinol 3 days prior to admission. Baseline labs on admission reveal unchanged creatinine clearance and uric acid values. She receives 20 mg venetoclax dose, and TLS labs in 6 hours reveal uric acid 7.8 mg/dL, potassium 1.2 × upper limit of normal and unchanged creatinine clearance, consistent with laboratory TLS. She is placed on a cardiac monitor, is noted to be in normal sinus rhythm, and receives rasburicase. Tumor lysis syndrome

labs in 6 hours reveal reduction in uric acid to 5.8 mg/dL and potassium at upper limit of normal, with continued stable creatinine clearance. Monitoring for TLS continues, with no further significant abnormalities, and venetoclax is held for 24 hours after normalization of laboratory values. She continues venetoclax dosing and remaining ramp-up doses with close monitoring and no other evidence of TLS.

NEUTROPENIA: ASSESSMENT AND MANAGEMENT

Neutropenia is another potentially life-threatening complication of antineoplastic therapy in patients with CLL. Neutropenia is a common adverse event in the majority of CLL therapies and results in an increased risk of infection (NCCN, 2020b). Neutropenia and neutropenic fever are characterized in Table 3. Neutropenia and/or neutropenic fever may lead to treatment disruption, delay, or discontinuation, and thus potentially negatively affect outcomes in patients with CLL.

Risk stratification for neutropenia is based on underlying disease and therapy regimen (NCCN, 2020b). Patients at low risk for neutropenia include most patients with solid tumors, with an expected length of neutropenia of fewer than 7 days. Chronic lymphocytic leukemia is included in the intermediate-risk group, along with autologous transplant, lymphoma, multiple myeloma, or purine analog–receiving patients, where a 7- to 10-day neutropenia length is expected. Although CLL is not high risk as a diagnosis, potential CLL therapies of allogeneic transplant with or without graft-vs.-host disease and alemtuzumab are considered high risk for neutropenia, along with acute leukemias, with an anticipated neutropenia length of more than 10 days (Table 4).

Prevention and Monitoring for Neutropenia

As with TLS, risk assessment, prevention, and monitoring for neutropenia are essential to maintaining patient safety and intended treatment schedules and doses. Close monitoring of laboratory values, patient education about signs and symptoms of infection and temperature monitoring at home, diligent assessment, and use of granulocyte colony-stimulating factors (G-CSF) are all critical to minimizing neutropenia and neutropenic fevers (NCCN, 2020b).

In addition, patients with CLL should be considered for prophylactic anti-infective agents (NCCN, 2020b). For patients receiving purine analog or bendamustine-based chemoimmunotherapy and/or alemtuzumab, herpes virus prophylaxis with acyclovir or equivalent and *Pneumocystis jiroveci* pneumonia prophylaxis with sulfamethoxazole/trimethoprim or equivalent are recommended during treatment and for a period of time thereafter. Hepatitis B virus and cytomegalovirus (CMV) prophylaxis should be considered in high-risk patients or in those testing positive for hepatitis B virus prior to anti-CD20 monoclonal antibodies. Specific to idelalisib therapy, infection concerns include fungal infections, hepatitis B virus, CMV, and varicella zoster virus, with consideration for CMV reactivation monitoring.

Signs and Symptoms

As patients with CLL prepare to initiate treatment, it is important that they are aware of signs and symptoms of infection, as well as when to report new or worsening signs and symptoms including fever, chills, sweats, change in cough or new cough, sore throat or new soreness in mouth or throat, shortness of breath, nasal congestion, stiff neck, burning or pain with urination, increased urination, diarrhea, vomiting, pain in abdomen or rectum, new onset of pain or changes in skin, urination, or mental status (AJMC, 2017; Lucas et al., 2018). Fever or pain may be the only indicator of an underlying infection. Patients with neutropenia and fever must be assessed for risk of severe infection immediately, making patient education and clear instructions on reporting to the health-care team key to prompt assessment.

Infections in patients with CLL are common due to the underlying disease and immunosuppressive therapies administered (NCCN, 2020a). The additional complexity in the infection picture

Table 3. Neutropenia and Neutropenic Fever

Neutropenia	Neutropenic fever
≤ 500 neutrophils/ μ L OR ≤ 1,000 neutrophils/ μ L and a predicted decline to ≤ 500/ μ L over the next 48 hours	A single temperature $\geq 38.3^{\circ}\text{C}$ (101°F) or $\geq 38.0^{\circ}\text{C}$ (100.4°F) for > 1 hour

Note. Information from NCCN (2020b).

Table 4. Risk for Infection by Disease/Therapy

	Low risk	Intermediate risk	High risk
Anticipated neutropenia	< 7 days	7-10 days	> 10 days
	Most solid tumors	Autologous HCT Lymphoma Multiple myeloma CLL Purine analog therapy (fludarabine)	Allogeneic HCT Acute leukemia GVHD Alemtuzumab

Note. CLL = chronic lymphocytic leukemia; GVHD = graft-vs.-host disease; HCT = hematopoietic stem cell transplantation. Information from NCCN (2020b).

for patients with CLL is the progressive reduction of immunoglobulin levels, thereby further increasing the risk for infection. Hypogammaglobulinemia is seen in approximately 40% of patients up to 3 years before the diagnosis of CLL. Immunoglobulin replacement therapy is recommended for IgG levels < 500 mg/dL. IgG levels should be monitored intermittently, particularly if recurring infections are noted (NCCN, 2020a).

Risk Assessment

Infection risk assessment begins with completion of the Multinational Association of Supportive Care in Cancer (MASCC) Risk Index to identify patients with cancer at low risk for febrile neutropenia (Klastersky et al., 2000; Lucas et al., 2018; Table 5). A MASCC score of > 21, along with an expected neutropenia duration of < 7 days in a patient who is clinically stable, without significant comorbidities, and has good overall performance status, reflects a low risk for infection during febrile neutropenia. Patients at high risk for infection during febrile neutropenia are those with a MASCC score ≤ 21, neutropenia duration ≥ 7 days or absolute neutrophil count ≤ 100 cells/μL, are clinically unstable, have comorbidities, renal or hepatic insufficiency, poor performance status, and advanced age (AJMC, 2017; Freifeld et al., 2011; Lucas et al., 2018).

In addition to the risk assessment outlined in Table 5, treatment intensity, treatment intent, and patient factors are also considerations in a febrile neutropenia risk assessment (NCCN, 2020b). Treatment intensity refers to high-dose therapy, dose-dense therapy, or standard dose therapy, with standard dose therapy conferring the lowest risk. Treatment undertaken with curative intent is

typically more aggressively managed to stay on the intended schedule and at full dose when compared with palliative therapy. High-risk patient features include prior chemotherapy or radiation therapy, persistent neutropenia, bone marrow involvement by tumor, recent surgery and/or open wounds, liver or kidney dysfunction, and age > 65 years receiving full-dose chemotherapy. For patients at high risk, broad-spectrum antibiotic prophylaxis should be considered, as well as prophylactic growth factor support with G-CSF. Granulocyte colony-stimulating factor prophylaxis is recommended for any antineoplastic regimen or agent with a febrile neutropenia incidence of > 20%. In CLL, purine analog or bendamustine-based chemoimmunotherapy are some of the treatments with > 20% incidence of febrile neutropenia, where prophylactic G-CSF is recommended (Sandoz, 2010; Teva Pharmaceuticals USA, Inc., 2019).

Table 5. MASCC Risk Index Factors and Weights

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms	5
No hypotension (systolic BP > 90 mm Hg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age < 60 yr	2

Note. MASCC = Multinational Association of Supportive Care in Cancer; BP = blood pressure. Information from Klastersky et al. (2000)

Initial Evaluation, Examination, and Assessment of Labs

If fever and neutropenia occur, the evaluation should include a complete history and physical examination (NCCN, 2020b). A full history of recent travel or infectious exposures is critical. Laboratory evaluation should include a complete blood cell count and blood chemistries, including electrolytes and liver function. Blood cultures and other appropriate microbiologic evaluation, such as urine culture, are also appropriate. Chest radiology or other appropriate imaging based on history and physical examination findings should be considered (Freifeld et al., 2011; Lucas et al., 2018).

Management According to Low or High Risk

Determination of risk is important in determining next steps (NCCN, 2020b). For low-risk patients, defined as an expected neutropenic period with neutrophils of $\leq 1,000$ cells/ μL for fewer than 7 days, patients may be treated at home, in an ambulatory clinic, or in the hospital. Laboratory and radiology results, history and physical examination findings, and financial/psychosocial considerations play important roles in choosing the most appropriate treatment approach. Options include up to 12 hours of observation in an ambulatory or short stay setting, IV antibiotics at home, daily infusion of long-acting anti-infective agent with or without oral antibiotics at home or in an infusion center, or oral antibiotics only for patients without nausea and vomiting, able to tolerate oral medications, and not on prior fluoroquinolone prophylaxis. These patients should be monitored daily (Freifeld et al., 2011).

For high-risk patients, defined as expected neutropenic period with neutrophils of $\leq 1,000$ cells/ μL for more than 7 days, the majority of patients should be treated with IV anti-infectives in the hospital (Freifeld et al., 2011; Lucas et al., 2018; NCCN, 2020b). There may be select patients in whom oral antibiotics with daily outpatient monitoring may be appropriate. Anti-infective therapy should continue at least until neutrophil count is ≥ 500 cells/ μL and rising.

Role of G-CSF

For patients in whom neutropenic fever develops and who are not receiving G-CSF or prophylac-

tic anti-infectives, clinicians may consider adding both (AJMC, 2017). In addition, antineoplastic regimen interruptions, dose reductions, or discontinuation may be appropriate. A review of prescribing information and/or clinical trial publications should be performed to ensure appropriate antineoplastic dosing after neutropenic fever.

Case Study 3

Mr. H is a 51-year-old male with newly diagnosed symptomatic CLL preparing to undergo fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy. He is otherwise healthy, and his pre-rituximab hepatitis B screening is negative.

His neutropenia risk is intermediate due to his diagnosis of CLL and planned treatment with fludarabine. Fludarabine-based chemoimmunotherapy is associated with a more than 20% incidence of febrile neutropenia; therefore, Mr. H should receive G-CSF prophylaxis. In addition, due to the high rate of infection with this regimen and according to prescribing information, he will receive anti-infective prophylaxis with acyclovir and sulfamethoxazole/trimethoprim against herpes zoster and *Pneumocystis jiroveci* pneumonia.

He is educated on neutropenia precautions, fever monitoring at home, the importance of prophylactic anti-infectives, signs and symptoms of infection, reporting to the health-care team, and laboratory monitoring and visit schedule.

Mr. H goes on to receive 6 cycles of full-dose FCR, with neutropenia reported in each cycle but no neutropenic fevers.

SUMMARY

Tumor lysis syndrome and neutropenia are important considerations in the management of patients with CLL. Tumor lysis syndrome and neutropenia with fever are both oncologic emergencies and require prompt and aggressive intervention. Comprehensive risk assessment, prophylaxis, monitoring, intervention, and patient education are important to ensure positive patient outcomes. Oncology advanced practitioners are in a unique position to plan for, educate patients on, and monitor for TLS and neutropenia to avoid complications that may lead to dose delays, dose reductions, therapy discontinuation, or even death in patients with CLL.

A pocket reference guide developed in conjunction with this article can be found on [advancedpractitioner.com](https://www.advancedpractitioner.com). It serves as a portable, educational resource for the interprofessional healthcare team, includes key practice considerations from the education provided, and can be used as a teaching tool at the point of care. ●

Disclosure

Ms. Goodrich has served a consultant for Janssen Oncology.

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