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INITIATING VENETOCLAX TREATMENT: CLINICAL PRACTICE PEARLS

Introduction

Overexpression of BCL-2 has been demonstrated in chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) cells where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics. Venetoclax is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. Based on evidence demonstrating improvement in progression-free survival (PFS) and overall survival (OS),¹⁻³ it has been approved in Canada for various regimens in the treatment of CLL and AML (i.e., venetoclax monotherapy, venetoclax/obinutuzumab and venetoclax/rituximab for CLL and venetoclax/azacitidine for AML). Initiation of venetoclax can be complicated as it requires ramp-up dosing with bloodwork and hydration to reduce the risk for tumor lysis syndrome (TLS). This article will focus on providing guidance during the initiation of venetoclax, particularly in resource limited centres.

Patient Preparation

The basis for successful treatment is dependent on how well a patient is informed about their treatment plan. It should be noted that when following the ramp up schedule with frequent lab monitoring, most patients can be managed effectively as outpatients with TLS largely being limited to those with biochemical aberrations. TLS is more prevalent in the CLL population than the AML population. During the initiation of venetoclax, patients will require multiple visits (daily or weekly depending on the protocol) for bloodwork and hydration, which can be particularly challenging for

patients in rural areas who must arrange transportation and accommodation. Social workers are a valuable resource for connecting patients with assistance programs to help cover the costs of transportation and accommodation. It is important to provide patients with both written and verbal information on the venetoclax schedule, as well as information on side effects management. When venetoclax is used in combination with other agents, patients are provided with a written medication calendar outlining the required supportive pre-medications.

Standard Protocol to Prevent Subjective Variation

Initiating venetoclax requires a multidisciplinary approach. It is prudent that each team member follows the same protocol to reduce the chance of error. We follow the Alberta Health Services protocols for venetoclax initiation at our centre. Standardized protocols aid in minimizing the risk of error when various nurses see the patient at each visit.

Assessment for the Risk of Tumor Lysis Syndrome (TLS)

Clinical TLS is defined by clinical manifestations, most commonly renal, cardiac or neuromuscular, induced by worsening of the metabolic and electrolyte abnormalities in laboratory test results.⁴ The risk of TLS depends on the initial lymphocyte count and the extent of lymphadenopathy (**Figure 1**).⁶ Due to the limitations of physical examinations, it is recommended to arrange a CT scan of neck, chest, abdomen, and pelvis to better assess overall lymphadenopathy.⁵ In addition, renal function is an important predictor for TLS, and patients with creatinine

clearance <80 mL/min are at relatively higher risk of developing TLS.⁷

Supportive Medications and Drug Interactions

1. Anti-infective prophylaxis:

The incidence of opportunistic infections with venetoclax is approximately 3.1%.⁸ The British Columbia Cancer Agency (BCCA) drug manual and product monograph for venetoclax do not recommend pneumocystis jirovecii pneumonia (PJP) and/or shingles prophylaxis. The BCCA protocol for venetoclax/obinutuzumab recommends PJP and anti-viral prophylaxis for lymphoma patients only during periods of grade 3/4 neutropenia.⁹ Due to the lack of strong evidence, many centers have their own protocol for anti-PJP and anti-shingles prophylaxis. For AML patients, anti-infective prophylaxis for bacterial, viral, and fungal infections is considered for all patients with an ANC of

<500/ μ L.⁹ PJP prophylaxis includes sulfamethoxazole and trimethoprim. For patients allergic to the sulfa group of drugs, dapsone or atovaquone are other alternatives. For shingles prophylaxis, we use valacyclovir. Hepatitis B screening is recommended prior to initiating chemo/immunotherapy.⁹

2. TLS prophylaxis:

All patients require prophylaxis for TLS using oral hydration and anti-hyperuricemia agents in an outpatient setting beginning 48 and 72 hours prior to initiation of therapy, respectively. Hospitalization is recommended for high-risk patients, medium risk patients with abnormal CrCl, and any at-risk patients with CrCl $\leq$ 50 mL/min. Hospitalization may be considered for those with additional risk factors for TLS (CrCl $\leq$ 80 mL/min; unable to drink 1.5-2 L per day; unsuitable for outpatient treatment and lab monitoring; or at physician discretion).⁹

3 STEPS: ASSESS, PREPARE, INITIATE

The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debunk) and decrease the risk of TLS

STEP 1: ASSESS PRIOR TO VENETOCLAX	STEP 2: PREPARE 2-3 DAYS PRIOR TO FIRST DOSE	STEP 3: INITIATE FIRST 5 WEEKS OF TREATMENT
Treatment: Tumor burden assessment; blood	Anti-hyperuricemics ^a	Hydration ^b
LOW TUMOR BURDEN All LN <5 cm AND ALC <25 $\times$ 10 ⁹ /L	 Allopurinol	Oral (1.5-2 L) 
MEDIUM TUMOR BURDEN Any LN 5 cm to <10 cm OR ALC $\geq$ 25 $\times$ 10 ⁹ /L	 Allopurinol	Oral (1.5-2 L)  Consider additional IV
HIGH TUMOR BURDEN Any LN $\geq$ 10 cm OR Any LN $\geq$ 5 cm AND ALC $\geq$ 25 $\times$ 10 ⁹ /L	 Allopurinol Consider rasburicase if baseline uric acid is elevated	Oral (1.5-2 L)  and IV (150-200 mL/hr as tolerated) 
		Outpatient • For first dose of 20 mg and 50 mg: predose, 6-8 hours, 24 hours • For subsequent ramp-up doses: predose Outpatient • For first dose of 20 mg and 50 mg: predose, 6-8 hours, 24 hours • For subsequent ramp-up doses: predose • For first dose of 20 mg and 50 mg: consider hospitalization for patients with CrCl <80 mL/min; see below for monitoring in hospital In hospital • For first dose of 20 mg and 50 mg: predose, 4, 8, 12, and 24 hours Outpatient • For subsequent ramp-up doses: predose, 6-8 hours, 24 hours

Step 1: Assess tumor burden, renal function, and comorbidities (CrCl <80 mL/min), and assess and correct baseline blood chemistries^a

Step 2: Begin administering antihyperuricemics 2-3 days prior and initiate oral and/or IV hydration 2 days prior^b

Step 3: Initiate 5-week dose ramp-up^c and monitor blood chemistry (review in real time). For 1L treatment, initiate the ramp-up on cycle 1, day 22^d

The risk of TLS may decrease as tumor burden decreases

Figure 1. TLS risk categories and prophylactic measures for venetoclax-based treatment in CLL⁶

Rasburicase can be considered for high-risk patients with an elevated uric acid level at baseline. With appropriate out-patient support, most patients do not need hospitalization for bloodwork.

3. Drug interactions:

CYP3A4 inducers may decrease serum concentration of venetoclax. P-glycoprotein inhibitors (P-gp) may increase serum concentration of venetoclax.^{10,11} Dose adjustment for venetoclax is necessary, especially in the treatment of AML in combination with azacitidine, to reduce the risk of severe cytopenia (primarily neutropenia). For the management of CLL, concurrent administration of therapeutic agents which are strong CYP 3A4 inhibitors is contraindicated at initiation and during the dose ramp-up phase due to increased serum concentration of venetoclax and potential increased risk of TLS.

Initiating Venetoclax: Ramp-up Phase:

During the early development of venetoclax in CLL, TLS events led to two deaths prior to adoption of the current 5-week ramp-up period: one death after an initial 50 mg venetoclax dose,¹² and one following a 1,200 mg dose.¹⁴ To mitigate TLS risk, modifications including TLS risk-stratification, prophylaxis, monitoring, and initiating with a lower dose (20 mg) were introduced to subsequent clinical protocols.⁸

For the venetoclax/rituximab (V/R) protocol, venetoclax is administered first and is titrated weekly starting at 20 mg upon initiation and increased up to 400 mg daily by week 5. Rituximab is initiated after the patient has completed the 5-week ramp-up of venetoclax.¹² The venetoclax/obinutuzumab protocol requires the initiation of venetoclax on Day 22 of cycle 1 after first administering obinutuzumab.¹³ Many of these patients will have had significant cytoreduction with obinutuzumab, making the ensuing venetoclax dose titration much easier. In an ongoing venetoclax and obinutuzumab trial involving patients with CLL and comorbid conditions, all documented TLS cases were in the obinutuzumab arm of the regimen prior to the initiation of venetoclax therapy. The weekly ramp up-protocol is the same as with V/R. Due to the more acute nature of AML compared to CLL, the venetoclax dose ramp-up is condensed to 3 days in combination with azacitidine.³

Side Effects Management

1. Tumor lysis syndrome:

Monitoring laboratory investigations for TLS and the management of abnormalities during venetoclax-based therapy is performed differently at various centres depending on the available resources.

In tertiary centres with available services, the pharmacy team is often utilized for monitoring and management of TLS-related issues. In centres where resources are limited, a team-based approach, led by the treating physician is often utilized.

For abnormal blood chemistry including elevated potassium; low calcium; elevated phosphate; elevated uric acid and/or elevated creatinine, the recommendation is to withhold venetoclax and the associated drug in the treatment regimen for CLL. Blood chemistry abnormalities must be corrected prior to its administration. If they resolve within 24-48 hours venetoclax may be re-initiated with the associated drug in the regimen.⁹ Mild aberrations in chemistry are common and can be followed if no clinical concern of TLS is present.

For abnormal blood chemistry lasting more than 48 hours or in the case of clinical TLS (the presence of laboratory TLS plus any of the following: cardiac arrhythmia; symptomatic hypocalcemia seizures; increased creatinine level of 26.5 μM ; or a single value greater than 1.5 times the upper limits of normal), the BCCA protocol recommends withholding the venetoclax-based regimen. Once the abnormalities have been corrected, venetoclax may be re-initiated at a lower dose as shown in **Table 1**. Reduced dosing is continued for 1 week before dose escalation can resume.⁹

Venetoclax Dose at Interruption	Recommended Restarting Dose
20 mg once daily	10 mg once daily
50 mg once daily	20 mg once daily
100 mg once daily	50 mg once daily
200 mg once daily	100 mg once daily
300 mg once daily	200 mg once daily
400 mg once daily	300 mg once daily

Table 1. Dose modification for venetoclax during ramp-up phase for clinical TLS⁹

2. Neutropenia/Pancytopenia

In clinical trials, when venetoclax was administered in combination with rituximab or obinutuzumab, the rates of grade 3/4 neutropenia were 57.7% and 52.8%, respectively.^{12,13} In patients with AML who received venetoclax/azacitidine, the incidence of

grade ≥ 3 neutropenia (absolute neutrophil count (ANC) $<1000/\mu\text{L}$) was 42%.³

In CLL, the recommended management of the first episode of grade 3 neutropenia and fever or grade 4 neutropenia (ANC $< 500/\mu\text{L}$) is to withhold venetoclax until the neutropenia resolves; venetoclax can then be re-initiated at the same dose. If neutropenia recurs, venetoclax should be withheld again until the neutropenia resolves. Venetoclax should then be re-initiated at a lower dose as recommended in **Table 1**. A dose escalation should be attempted if the neutrophil count remains normal for 1 week.³ If grade 3 neutropenia persists, the use of granulocyte colony stimulating factor (G-CSF) may be considered often at dosing schedules of 300 μg subcutaneously, one to two times per week.

For AML-related treatment with venetoclax and azacitidine, neutropenia management depends on the remission status of the AML. AML patients with residual disease on bone marrow following cycle 1 should receive subsequent cycles of treatment with no dose interruption/delay until a repeat assessment demonstrates complete remission (CR). For patients with CR and grade 4 pancytopenia (ANC $<500/\mu\text{L}$, platelets $<25 \times 10^3/\mu\text{L}$) following cycle 1, venetoclax must be delayed until ANC and platelet count recovery or for up to 14 days. For subsequent cycles after achieving CR, patients with grade 4 pancytopenia must have the next cycle delayed until ANC and platelet count recovery is achieved or for up to 14 days. Venetoclax is administered for 21 days instead of 28 days for subsequent cycles.^{3,11}

Use in Special Populations

Pregnancy and lactation

Venetoclax should not be used during pregnancy. Females of reproductive potential should undergo pregnancy testing prior to the initiation of venetoclax. Females of reproductive potential should be advised to use effective contraception during treatment with venetoclax and for at least 30 days following the last venetoclax dose.¹⁵ Breastfeeding should be discontinued during treatment with venetoclax.¹⁵

Vaccines

Live or attenuated vaccines are not recommended during venetoclax treatment and until B-cell recovery has occurred following treatment (i.e., at least 6 months after treatment with an anti-CD20 monoclonal antibody and at least 3 months after other treatment is discontinued).⁹

Conclusion

Venetoclax has offered a new and effective option in targeted therapy for CLL and AML. Venetoclax initiation and ramp-up require TLS risk assessment, and risk-stratified monitoring and mitigation measures, which can be cumbersome but allow for universally safe initiation and dose escalation. As an oral therapy with good tolerability, it is an attractive option for the elderly patient population. An all-inclusive approach involving a well-informed patient and a multi-disciplinary medical team has the potential to help patients overcome possible initial hurdles in the long-term treatment of AML and CLL.

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References

1. Al-Sawaf O, Zhang C, Tandon M, Sinha A, Fink AM, Robrecht S, Samoylova O, Liberati AM, Pinilla-Ibarz J, Opat S, Sivcheva L. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology*. 2020 Sep 1;21(9):1188-200.
2. Kater AP, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Owen C, Assouline SE, Lamanna N, Robak TJ, de la Serna J, Jaeger U. Five-year analysis of murano study demonstrates enduring undetectable minimal residual disease (uMRD) in a subset of relapsed/refractory chronic lymphocytic leukemia (R/R CLL) patients (Pts) following fixed-duration venetoclax-rituximab (VenR) therapy (Tx). *Blood*. 2020 Nov 5;136:19-21.
3. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letai A, Fenaux P, Koller E. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *New England Journal of Medicine*. 2020 Aug 13;383(7):617-29.
4. Cairo MS, Coiffier B, Reiter A, Younes A, TLS Expert Panel. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *British journal of haematology*. 2010 May;149(4):578-86.
5. Fischer K, Al-Sawaf O, Hallek M. Preventing and monitoring for tumor lysis syndrome and other toxicities of venetoclax during treatment of chronic lymphocytic leukemia. *Hematology* 2014, the American Society of Hematology Education Program Book. 2020 Dec 4;2020(1):357-62.
6. Waggoner M, Katselos J, Thomas E, Galinsky I, Fox H. Practical Management of the Venetoclax-Treated Patient in Chronic Lymphocytic Leukemia and Acute Myeloid Leukemia. *Journal of the Advanced Practitioner in Oncology*. 2022 May;13(4):400.
7. Davids MS, Hallek M, Wierda W, Roberts AW, Stilgenbauer S, Jones JA, Gerecitano JF, Kim SY, Potluri J, Busman T, Best A. Comprehensive Safety Analysis of Venetoclax Monotherapy for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia Safety of Venetoclax Monotherapy in Relapsed/Refractory CLL. *Clinical Cancer Research*. 2018 Sep 15;24(18):4371-9.
8. BC Cancer Protocol Summary for Treatment of Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma using Venetoclax and Obinutuzumab. http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Lymphoma-Myeloma/LYVENOB_Protocol.pdf.
9. Wei AH, Montesinos P, Ivanov V, DiNardo CD, Novak J, Laribi K, Kim I, Stevens DA, Fiedler W, Pagoni M, Samoylova O. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020 Jun 11;135(24):2137-45.
10. Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, Owen C, Gerecitano J, Robak T, De la Serna J, Jaeger U. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *New England Journal of Medicine*. 2018 Mar 22;378(12):1107-20.
11. Fischer K, Al-Sawaf O, Bahlo J, Fink AM, Tandon M, Dixon M, Robrecht S, Warburton S, Humphrey K, Samoylova O, Liberati AM. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *New England Journal of Medicine*. 2019 Jun 6;380(23):2225-36.
12. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *New England Journal of Medicine*. 2015 Oct 22;373(17):1627-39.
13. Venclexta® Product Monograph. https://pdf.hres.ca/dpd_pm/00046366.PDF