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WITH GREAT POWER COMES GREAT RESPONSIBILITY: MANAGING SIDE EFFECTS OF NOVEL TREATMENTS IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

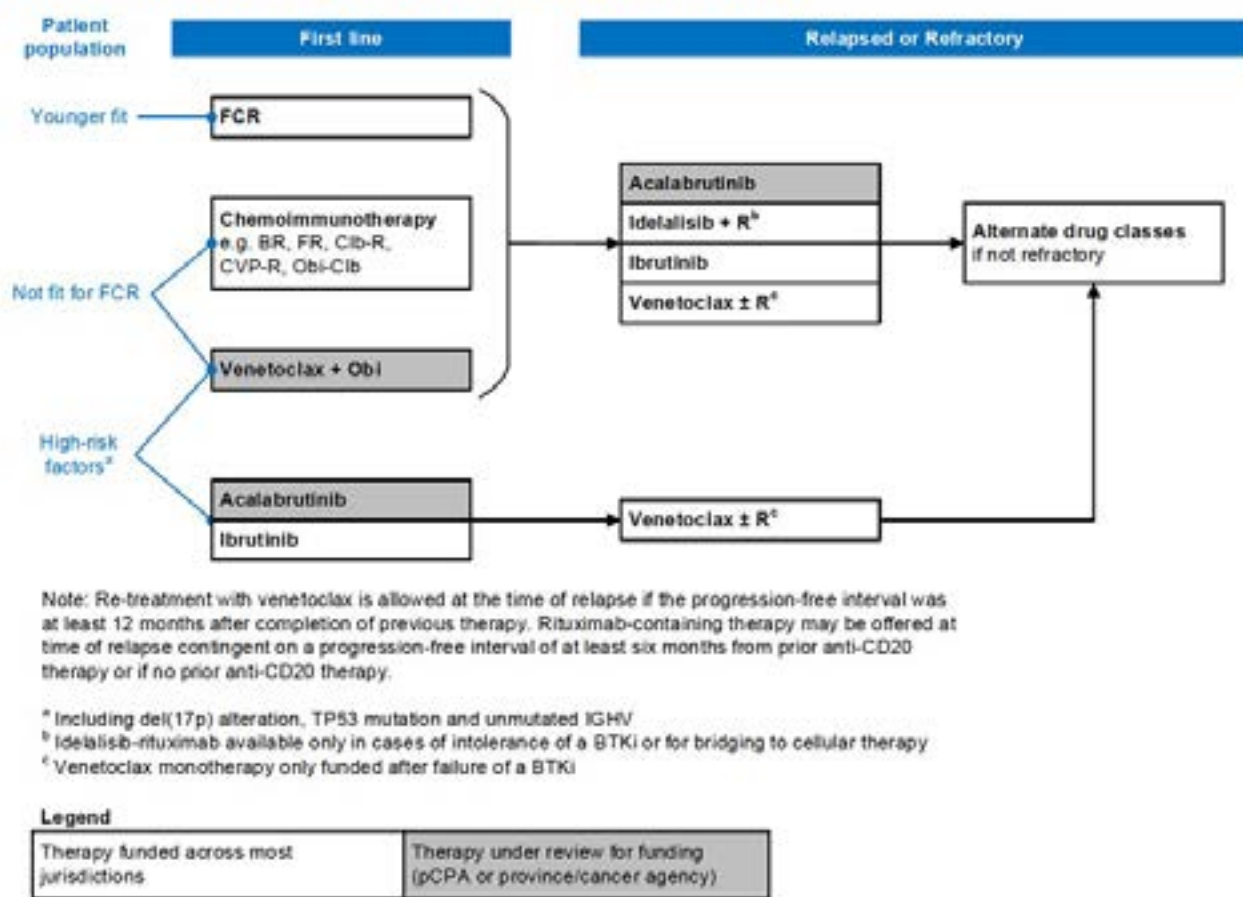
The treatment paradigm shift in CLL has uprooted many clinicians' standard practices. Previously, treatment largely depended on age, organ function and "fitness" based on clinical trials which used CIRS (cumulative illness rating scale) scores¹. Today, as a hematologist who mainly treats patients with CLL, treatment strategies are more complex and multi-factorial. Treatments are based on molecular profiling, which aids in the identification of lower-risk patients for time-limited treatment² options versus higher-risk patients (IGHV unmutated³, del 17p or TP534) who benefit from continuous therapies^{5,6}. The highest-risk patients can be identified using a staging system for CLL known as the CLL-International Prognostic Index (CLL-IPI)⁷⁻¹⁰. However, increased CIRS scores are prognostic for poor outcomes independent of the CLL-IPI¹¹. As a result, selecting the right treatment for the right individual has never been more important, especially in the era of novel therapeutics. This treatment selection decision pathway includes understanding both patient factors and medical factors that may influence patient outcomes.

Novel time-limited treatment options in Canada at this time include venetoclax and obinutuzumab² combination therapy for patients who are deemed "unfit" for FCR (fludarabine, cyclophosphamide, rituximab) in the frontline setting and venetoclax and rituximab¹² in the relapsed setting. Venetoclax can also be used as monotherapy¹³ in the relapsed setting (**Figure 1**).

In the front-line setting obinutuzumab is the monoclonal antibody in the VenO regimen. It can cause TLS, infusion related reactions, neutropenia, and febrile neutropenic events^{2,14-18}. Venetoclax, is an oral agent delivered following obinutuzumab administration on Cycle 1 Day 22 continuing through Cycle 2 Day 28¹⁸. One of the major challenges in the treatment of CLL with venetoclax involves the assessment of tumour lysis syndrome (TLS) risk (**Figure 2**).

Venetoclax is initiated at a starting dose of 20 mg once daily for 7 days and then titrated to a weekly ramp-up schedule of 400 mg over a period of 5 weeks. The TLS monitoring requirements recommend bloodwork 3 days a week to ensure no evidence of TLS after each dose escalation¹⁸. Blood chemistry monitoring should be performed for all patients at 6 to 8 hours post-dose, and 24 hours post-dose for the first dose of 20 and 50 mg, and pre-dose at subsequent ramp-up doses. The next dose should not be administered until 24-hour blood chemistry results have been evaluated.

Since the risk of developing TLS is highest when treatment is initiated and the overall tumor mass is highest, debulking may be warranted. Our center will often pre-treat patients with a dose of 10 mg for a week to help reduce the risk of TLS and extend the ramp-up schedule to 6 weeks. The use of pharmacological agents as part of a debulking strategy should be considered in certain scenarios to improve



B = bendamustine; BTKi = Bruton's tyrosine kinase inhibitor; C = cyclophosphamide; Cib = chlorambucil; CLL = chronic lymphocytic leukemia; F = fludarabine; IGHV = immunoglobulin heavy-chain variable region gene; Obi = obinutuzumab; R = rituximab; V = vincristine.

Figure 1. Treatment algorithm for CLL; CADTH Reimbursement Review Provisional Funding Algorithm; May 2021

the tolerability and safety of first treatment cycles with chemoimmunotherapy. Some data shows that obinutuzumab reduces the TLS risk from high risk to moderate risk when a debulking strategy is initiated¹⁸. The ramp-up can also be shortened in the inpatient setting if required especially in a second line setting when patients are rapidly progressing off a Bruton's Tyrosine Kinase Inhibitor (BTKi)¹⁹ to gain control rapidly.

A similar approach applies in the relapsed setting. In relapse, rituximab is administered after the venetoclax, in cycle 2 and thus minimal debulking pre-ramp-up occurs. The total duration of rituximab therapy in combination with venetoclax is 6 months, a similar duration with obinutuzumab in the frontline setting. However, the treatment duration of venetoclax is 24 months in relapse setting instead of 12 months as administered with obinutuzumab front line. Other side effects commonly experienced ($\geq 20\%$ of any Grade) with the use of venetoclax as monotherapy are neutropenia, diarrhea, nausea, anemia, thrombocytopenia, fatigue, upper respiratory tract infection and cough. The most common

($\geq 20\%$) adverse reactions of any grade reported in patients receiving venetoclax in combination with obinutuzumab were neutropenia, and diarrhea. The most common ($\geq 5\%$) Grade 3/4 reactions in the venetoclax + obinutuzumab patients were neutropenia, anemia, and febrile neutropenia.

There are a number of simple interventions available to manage adverse events related to venetoclax. The use of granulocyte colony-stimulating factor (G-CSF) in the setting of combination monoclonal anti-CD20 agent + venetoclax has been shown to be helpful especially in the frontline, when depth of response for optimal remission in a short period is the goal. In the past, the concern was that G-CSF use could mask marrow toxicity in combination with chemoimmunotherapy, thereby increasing the risk of MDS or secondary AML^{20,21}. Another approach to managing adverse reactions includes holding the venetoclax and dose reductions as shown in trials^{2,12}. Holding of the monoclonal antibody is not recommended unless there is a clinically significant event such as febrile neutropenia. These time-limited novel options benefit patients by providing them time off therapy^{2,12}. There are

MANAGEMENT OF VENETOCLAX-ASSOCIATED TOXICITIES	Tumor Lysis Syndrome		Debulking strategies	
	Laboratory TLS		Prior to Ven ramp-up	
	• Potassium ↑ • Uric acid ↑ • Phosphate ↑ • Calcium ↓		• Chemotherapy (e.g. 2x bendamustine) - or • Anti CD20 antibody (e.g. 3x obinutuzumab) - or • BTK inhibitor (e.g. 3 months ibrutinib)	
	Clinical TLS • Creatinine ↑, cardiac arrhythmia, seizure			
Neutropenia	Risk assessment		Risk mitigation	
In cases of grade 3 or 4 neutropenia or febrile neutropenia • Pause venetoclax, resume when resolved to at least grade 1 • Use GCSF when clinically indicated 	Low All LN <5 cm AND ALC <25 G/l		Allopurinol (or rasburicase) Oral hydration	
	Intermediate Any LN 5–10 cm OR ALC ≥ 25 G/l		Allopurinol (or rasburicase) Oral / IV hydration	
	High Any LN ≥10 cm OR Any LN ≥5 cm AND ALC ≥25 G/l		Allopurinol (or rasburicase) IV hydration Consider hospitalization	

Figure 2. Preventing and monitoring for tumor lysis syndrome and other toxicities of venetoclax during treatment of chronic lymphocytic leukemia; adapted from Fischer et al

fewer side effects related to cardiac and skin toxicities but diarrhea and or constipation may occur.

Venetoclax administered as monotherapy may also be considered when high risk patients progress on continuous therapy with BTKi or when patients do not tolerate BTKi due to their toxicity profile¹³. It is important to note that in both the CLL¹⁴ trial and in retrospective reviews of real-world clinical practice, only 80–85% of patients achieved dose escalation to the maximum recommended dose of 400 mg daily²². In some studies, rates of neutropenia with venetoclax monotherapy in the relapsed setting were 47%²² and in the CLL¹⁴ setting it was 53%². Thrombocytopenia was observed in greater than one-third of cases in both real world evidence and trial settings^{2,22}. These toxicities were managed by either dose holds or dose reductions². Febrile neutropenic episodes (FNE) occurred in 10–12% of patients, and may be managed with the use of G-CSF^{2,22}.

BTK inhibitors have changed the treatment landscape for patients with high-risk CLL. They have been used in salvaging patients in relapse who were initially treated with chemotherapy²³. In addition, their widespread uptake in the frontline has spared many patients from treatments that are not efficacious^{24–26}. Published toxicities²⁷ associated with BTKi use include off target effects such as skin rashes, folliculitis, panniculitis, paronychia due to the on target endothelial growth factor receptor effects, gastrointestinal effects commonly associated with interleukin-2–inducible T-cell kinase (ITKs), and non-thrombocytopenia-associated bleeding due to inhibition of platelet aggregation^{28,29}. Arthralgias have also been reported in studies and in the real world^{23,29,30}. It is important for clinicians to be aware that significant variation may exist between rates of adverse effects documented in the initial pivotal studies using BTKi and in a real-world settings. Real-world data has shown differing rates of dose reductions or discontinuation (increased) in the frontline and relapsed

settings. Over time cardiac events, including atrial fibrillation, hypertension, ventricular arrhythmias and sudden death have been associated with the use of BTKi^{29,31} and may be due to off-target effects. A 140 mg dose of ibrutinib (1/3 of the prescribed dose) has been shown to enable 90% BTK inhibition. Although, it is hypothesized that some of the off-target effects of the drug in both blood and lymph nodes contribute to deep and lasting remission. That said, dose reductions or dose holds may also be used to offset these toxicities especially in low risk individuals^{32,33}. RWE studies corroborated this^{28,34}, and clinical trials also reported drug discontinuation as an option for the management of adverse reactions as demonstrated in the ECOG 1912 study²⁵. However, the risk of sudden death still remained^{25,31}. The rates of atrial fibrillation for ibrutinib have been reported to be in 10-20% range in both the real world^{25,28} and trial settings²⁴⁻²⁶. The next generation of BTKi are proving safer than ibrutinib. Where head-to-head data are available, decreased rates of atrial fibrillation and hypertension are observed for acalabrutinib^{35,36} (rates of 3-4% for all grades for both) and decreased rates of atrial fibrillation (1-3%) and similar rates of hypertension (10-13%) with zanubrutinib³⁷. Zanubrutinib has been associated with higher rates of neutropenia than ibrutinib, however due to the short period of follow up in clinical trial reporting (12 months), this toxicity profile needs further assessment³⁷.

Acalabrutinib is most often used in our center due to a decreased side effect profile and minimal risk of sudden death. Our center has rarely reported atrial fibrillation in our acalabrutinib patients however we may also be better at selecting patients for BTKi use. The discontinuation of a BTKi (due the atrial fibrillation) is not recommended in high-risk patients unless medical management of the atrial fibrillation is of concern. If a patient has been initiated on ibrutinib, clinicians may consider challenging the patient with a second-generation BTKi³⁸ before discontinuing this line of therapy. In lower risk individuals whose atrial fibrillation does not resolve and who require therapy, a switch to a BCL-2 inhibitor-based fixed-duration therapy is a viable treatment option. If the patient is low risk and has been on therapy for at least 22 months with ibrutinib, there is also the possibility of stopping treatment until disease relapses requiring re-initiation of treatment²⁵.

Patients on BTKi are at higher risk for developing hypertension. This may occur early or later in the course of therapy. Patients with undiagnosed hypertension should be assessed and co-managed with their primary care physicians. In those patients on established therapy, whose disease is well-controlled and who develop hypertension, dose reduction and engagement with primary care is warranted. Care coordination with cardio-oncology may also be a good resource if available. Second generation BTKi have also been associated with a lower incidence of

arthralgias³⁰ and bleeding but may produce drug-specific side effects such as headaches with acalabrutinib^{6,35}, which typically present within the first 12 weeks of initiation of therapy²⁹.

As we look to the future of novel therapies for the treatment and management of CLL, emerging agents such as pirtobrutinib portend a toxicity profile that is similar to current second generation BTKi in both BTKi-naïve and sensitive patients^{39,40}. Additional studies involving newer BTKi such as nemtabrutinib have the potential for even lower rates of cardiac events which may provide clinicians with further tools in their therapeutic armamentarium to optimize safety and efficacy outcomes for CLL patients.

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