HEMATOLOGY

CLL Treatment

CARE™ GUIDANCE 2022

VERSION 4.0

CONTENT AS OF DECEMBER 2022

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CARE™ CLL GUIDANCE 2022 VERSION

4.0 - CONTENT AS OF DECEMBER 2022

BACKGROUND

In July 2020, The CARE™ Hematology Faculty developed and published Considerations for Malignant Hematology Patient Management and Treatment During the COVID-19 Era. It was updated in January 2021. Changes in the delivery of care brought on by the pandemic, as well as recent drug approvals have prompted the CARE™ Faculty to update the CARE™ CLL Treatment Guidance.

This is the 4th iteration (V.4) of the CARE™ CLL Treatment Guidance. It aims to provide further context and guidance.

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CARE™ TREATMENT ALGORITHMS FOR FRONTLINE AND RELAPSED/REFRACTORY (R/R) CLL

Key Takeaways

- *Genetic disease drivers important for progression and treatment resistance / early relapse*
    - *IGHV mutational status and del 17p / TP 53 status*
- *Outcome improvement with targeted therapy, i.e. venetoclax, ibrutinib and acalabrutinib (+/- CD20 antibody) as compared to CIT*
    - *Outcomes most pronounced with unmutated IGHV, and 17p-/TP53mut CLL, but benefits still seen in good risk patients*
    - *Occasional young, fit, mutated patients may opt for FCR given long term FU and likely "cure" in many patients (note secondary MDS/AML risk)*
- *Improvement in PFS appears similar for all targeted approaches in cross trial comparison, but so far lack of comparative trials*
- *Choice of BCL2 / BTK targeting agent incorporates several factors:*
    - *Patient preference (treatment duration and monitoring)*
    - *Coexisting conditions (hypertension, cardiovascular, renal)*
    - *Concomitant medication (anticoagulants, antiplatelets, CYP3A)*
- *There is no clear preference of sequencing of BTKi and venetoclax-based therapies in the 1st and 2nd line*
    - *Specific patient choices are based on above*
    - *Given the especially high-risk nature of del(17p) / TP53 mutation, most experts still prefer indefinite therapy*

Future directions:

- *Combination BTKi and venetoclax +/- CD20 Ab is providing options for finite duration therapy with high levels of uMRD*
- *MRD testing may allow for adjusting therapies going forward*
- *Non-covalent BTKi including pirtobrutinib are showing high levels of activity in patients who are BTKi and venetoclax resistant*
- *Cellular therapies including CAR-T and bispecific Ab are evolving in CLL*

Considerations Prior to Initiation of Therapy

- *Conversation on treatment goals and the risk-benefit analysis of all appropriate treatment options should happen with all patients*
- *Choosing between Continuous and Fixed Duration Treatment*
    - *Individual patient preference, patient co-morbidity profile, long-term efficacy and safety, comfortability and/or resources available for managing drug administration, and cost analyses should be considered when choosing between continuous vs. fixed duration therapy*

Considerations for Management of Patients on Therapy

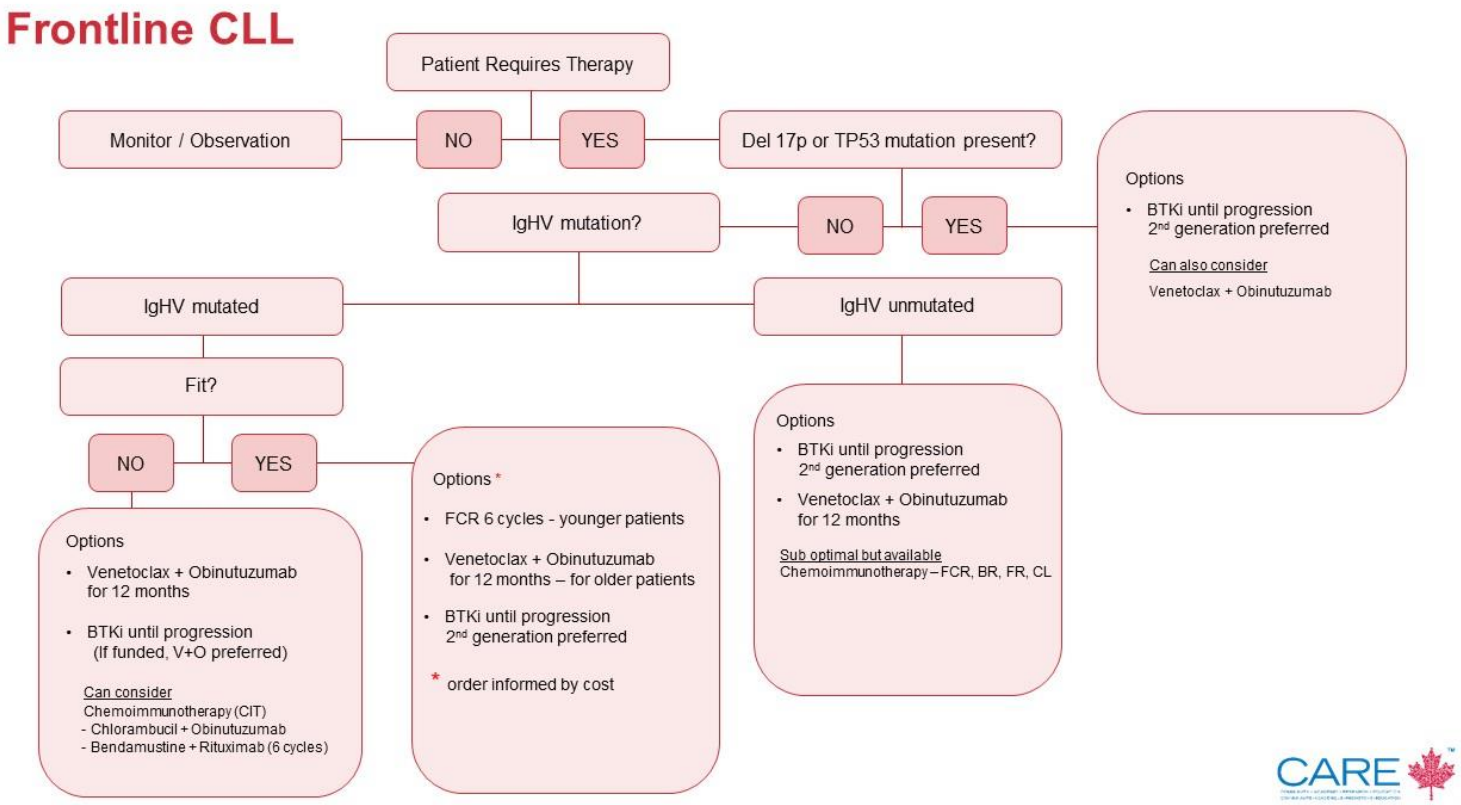
- Patient adherence to oral targeted therapies is less than optimal and is a major contributor to worse clinical outcomes
- Management of Adverse Events

Management of CLL Patients during COVID-19

- Therapeutic decisions should remain based on individual factors such as symptom burden and comorbidities, along with molecular and cytogenetics abnormalities.
- Patients should be vaccinated and consideration for pre-exposure prophylaxis to prevent COVID-19 in people who have moderate to severe immune compromise.

Richter Syndrome

- Richter syndrome (RS), also known as Richter transformation is defined as the transformation of CLL into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL). RS occurs in approximately 2% - 10% of CLL patients during the course of their disease, with a transformation rate of 0.5% - 1% per year.



(PATIENT) FACTORS IMPACTING CHOICE - BTKI VS VENETOCLAX-BASED THERAPY

BTKi may be preferred for patients with preference to oral only regimen.

- 2nd generation BTK inhibitors are better tolerated and no less effective than ibrutinib

Venetoclax may be preferred for patients with high risk for bleeding (including low platelets, known bleeding disorders, or anticoagulation); difficult to control hypertension; active/uncontrolled cardiac issues, and those with a preference to finite therapy.

Each of these factors/options must be considered in context of the individual patient and full clinical profile.

Given provincial budgetary constraints, *provinces* may prefer an effective time-limited option for cost-effectiveness reasons.

Additional Considerations

Patients should be monitored for Richter syndrome (RS) throughout treatment.
Clinical trials should be considered at all parts along patient pathway.

Supporting Studies

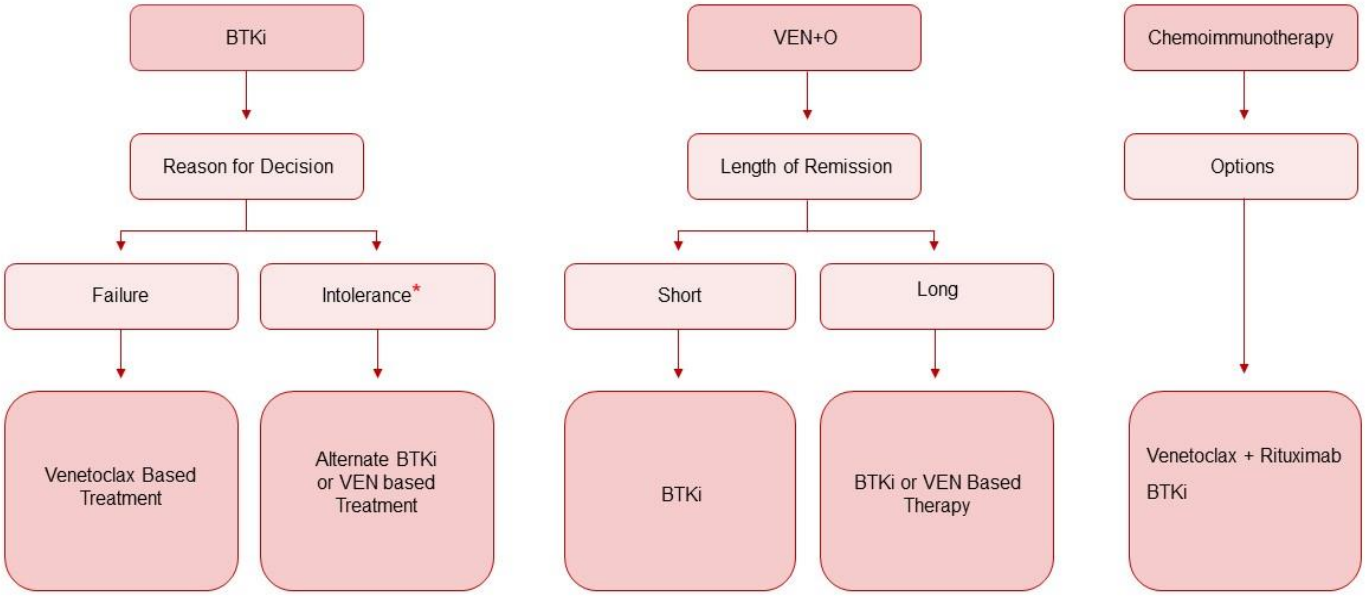
Ibrutinib
ALLIANCE A041202 (NCT01886872)
iLLUMINATE (NCT02264574)
ECOG-ACRIN, E1912 Study (NCT02048813)
UK FLAIR Trial

Acalabrutinib +/- Obinutuzumab
ELEVATE-TN Trial (NCT02475681)

Venetoclax + Obinutuzumab
CLL14 Trial (NCT02242942)

FCR
German CLL Study Group (GCLLSD)
CLL8 Study (NCT00281918)
CLL13/GAIA

R/R CLL – 1st Relapse



*If mutation testing is available and positive, VEN based preferred. (This test not generally available in Canada).

3RD LINE THERAPY

Will be dependent on previous therapy, response, and tolerance.

- Preference (at time of writing) is the use of BTK inhibitors or BTK2 (Venetoclax) based treatment, before considering other agents, including PI3K inhibitors. (Minimal value if progressed on BTKi).

Patients with high-risk disease and/or 3rd line treatment, who have relapsed after BTKi or VEN based therapy, should be considered for additional options.

- allo SCT
- Non-covalent BTK2
- CAR T-cell therapy
- Clinical trials, which include BiTE therapies

Additional Considerations

- Patients should be monitored for Richter syndrome (RS) throughout treatment
- Clinical trials should be considered at all parts along patient pathway

Supporting Studies

Ibrutinib
RESONATE (NCT01578707)

Acalabrutinib based regimen
ASCEND (NCT02970318)

Venetoclax based regimen
MURANO (NCT02005471)

Allotransplant
Donor SCT in High-Risk CLL (NCT01027000)

CAR T-cell Therapy
CAR T-cell Leukemia or Lymphoma, Resistant or Refractory to Chemotherapy (NCT01029366)

SUPPORTING INFORMATION/DISCUSSION

CONSIDERATIONS PRIOR TO INITIATION OF THERAPY

Benefits of Shared Decision Making

A conversation with patients on their treatment goals and the risk-benefit analysis of all appropriate treatment options should be offered to all patients, *even during the pandemic*.

Shared decision-making can:

- Allow for more personalized treatment
- Reduce patient and caregiver anxiety
- Improve adherence to treatment plans
- Improve health outcomes
- Increase patients' satisfaction

Consider discussing with the patient:

- What is important to them with their treatment (patient goals)
- Advantages and disadvantages of continuous vs fixed duration therapy
- Specific side effects of each therapeutic option
- Adherence
- Resources/Support programs available

Choosing between Continuous and Fixed Duration Treatment

Individual patient preference, patient co-morbidity profile, long-term efficacy and safety, comfortability and/or resources available for managing drug administration, and cost analyses should be considered when choosing between continuous and FTD. How clinicians prioritize new data that comes out, individual centre's policy, and regional differences in what is funded and accessible add complexity.

Considerations include:

- Oral Targeted Therapy (OTT) with a fixed duration of treatment could possibly prevent the emergence of resistant clones driven by continuous treatment with BTKi (most CLL patients progressing on ibrutinib harbour mutations in BTK or in PLCG2)
- Monitoring adherence is especially important with medications that have a continuous treatment duration
- Patients who have completed fixed duration regimens may appreciate no longer having a daily reminder that they have cancer
- Alternatively, some patients feel less anxiety and more in control of their cancer when taking daily medication
    - Patients can experience fear of relapse during treatment which may rise significantly after FTD ends

CONSIDERATIONS FOR MANAGEMENT OF PATIENTS ON THERAPY

Adherence to Oral Medications

Patient adherence to oral targeted therapies is less than optimal and is a major contributor to worse clinical outcomes and increased HCP fatigue and frustration. Even severity of disease state does not always translate to good adherence.

Determinants of non-adherence include:

- Low motivation
- Lack of perceived risk
- Poor patient-provider communication
- Concern over side effects

Adherence can be improved in many cases with nurse coaching through a patient support program and open communication on the risks associated with poor compliance with patients and caregivers.

CONSIDERATIONS FOR MANAGEMENT OF PATIENTS ON THERAPY *continued*

Management of Adverse Events

Common adverse events to watch for:

- Chemoimmunotherapy (CIT) - myelosuppression, infections, secondary malignancies
- BTKi - cardiac toxicity, bleeding and autoimmune disease
  - Cardiac toxicity should be co-managed in collaboration with a cardiology team
  - Strategies to discontinue therapy are of great interest and are being tested against continuous BTKi therapy in NA Intergroup trials in elderly (ALLIANCE) and younger (ECOG) patients
  - Newer BTKi have demonstrated less cardiac toxicity
- Venetoclax – Tumour Lysis Syndrome (TLS) and infections
  - A TLS Risk Stratification System based on tumour burden can be utilized to minimize risk and allow for more efficient utilization of resources
  - Neutropenia is commonly encountered in the first few weeks of venetoclax therapy- Low doses of GCSF can be used until normal hematopoiesis is established

For most patients, **treatment side effects are temporary and go away once therapy ends.**

CONSIDERATIONS FOR CLL TREATMENT DURING COVID-19

- Take into account local infection rates and risk to the patient of contracting COVID-19.
- Encourage patients to be current with approved COVID-19 vaccinations.
- Therapeutic decisions should remain to be based on individual factors such as symptom burden and comorbidities, along with molecular and cytogenetics abnormalities.
- **If patients are currently on OTT without complications, they should maintain on the same therapy.**
- **If a patient acquires COVID while on treatment, interrupt therapy when feasible,** delay until symptoms resolve and tests are negative. **Continuing with treatment may be warranted**.
- Healthcare professionals should be aware of their local variant proportions, discuss risk of contracting COVID-19 with immunocompromised individuals, and advise them to seek immediate medical attention if they develop COVID-19 symptoms.
  - EVUSHELD™, a monoclonal antibody, is authorized as pre-exposure prophylaxis to prevent COVID-19 in people who have moderate to severe immune compromise. EVUSHELD™ can also be used by those for whom vaccination with any available COVID-19 vaccine is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine(s) or its component(s).
    - Data suggests that EVUSHELD™ could have decreased efficacy against the Omicron BA.4.6, BF.7, and BA.2.75 sublineages with substitutions at spike protein 346.

RICHTER SYNDROME

Richter syndrome (RS), also known as Richter transformation is defined as the transformation of CLL into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL). RS occurs in approximately 2% - 10% of CLL patients during the course of their disease, with a transformation rate of 0.5% - 1% per year. For patients who develop DLBCL that is clonally related to the original CLL (approximately 80% of RS cases), chemoimmunotherapy or allotransplant could be treatment options. DLBCL that is clonally unrelated to the original CLL (approximately 20% of RS cases) can be treated like de novo DLBCL.

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The **mission** of the CARE™ Faculty is to enhance medical education, with the explicit goal of improving patient outcomes.

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