CARE™ CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) MANAGEMENT CONSIDERATIONS FOR ONTARIO 2020

MAY 2020
CARE™ Chronic Lymphocytic Leukemia (CLL) Management Considerations for Ontario 2020

Members of the CARE™ Hematology Faculty recently met at the CARE™ Winter Hematology Update (WHU) 2020 (February 2020, Toronto ON). As an extension of this meeting, CLL specific insights were discussed with select Faculty in conjunction with the WHU conference. The aim was to review relevant news and data from a Canadian perspective and provide insight on the potential impact to clinical practice as we move forward in 2020.

What follows is a distillation of perspectives discussed and augmented with supporting data and information from recent major events (i.e. ASH 2019) for currently available (approved) options.

To access full presentation content from WHU 2020 and additional education resources from the CARE™ Hematology Faculty please visit www.CAREeducation.ca

**CARE™ CLL Management Considerations for Ontario 2020 include:**

**Treatment Guidance and Supporting Studies**

**Front-line CLL**
- Fit Patients *(no del17p/, TP53 mutated, age < 65)*
- Unfit Patients *(no del17p/, TP53 mutated, age ≥ 65)*
- All Patients *(del17p, TP53 mutated)*

**Relapsed/Refractory CLL**
- Post-Chemoimmunotherapy (CIT)
- Post-Ibrutinib Failure

**Additional Clinical Considerations**
- Sequencing of Ibrutinib and Venetoclax
- Treatment Duration
- The Utility of Minimal Residual Disease (MRD)
- Novel Combination for First-line CLL *(Ibrutinib + Venetoclax)*

**CARE™ Response to COVID-19**

Canada’s health-care system is hard at work fighting COVID-19, but the 1 million Canadians living with cancer face an extra challenge. Treatments and tests may be altered or delayed and this patient group may be more vulnerable to COVID-19.

The current pandemic is forcing clinicians to react rapidly and develop solutions to deliver healthcare. In an effort to help understand clinician’s approach and needs, CARE™ Hematology Faculty have developed a short questionnaire with a focus on both today and the near term, with a commitment to review insights and provide guidance by June. (Tied into the annual CARE™ report on news and developments from ASCO and EHA).
TREATMENT GUIDANCE AND SUPPORTING STUDIES

FRONT-LINE CLL

Fit Patients (no del17p/ TP53 mutated, age < 65)

mIGHV
Fludarabine + cyclophosphamide + rituximab (FCR) (funded)
• Supported by ECOG E1912
Bendamustine + rituximab (BR) (>65) (not funded)
Ibrutinib (not funded)

uIGHV
Ibrutinib (funded)
• Supported by ECOG E1912

Key Study Highlights

ECOG E1912
At 45 months of follow-up both IR and FCR continue to demonstrate similar PFS in low risk (mutated IGHV) CLL patients. There is potential for long-term disease control with FCR. FCR remains a reasonable (and currently the only funded) option for low risk patients.

Updated E1912 data support ibrutinib as standard of care for front-line, high risk CLL patients and demonstrated a survival advantage for ibrutinib + rituximab (IR) over FCR. OS in the ITT population persists with long-term follow-up, with fewer IR patients experiencing grade 3-4 AE’s versus FCR.

All Patients (del17p, TP53 mutated)
Ibrutinib (funded)
• Supported by RESONATE and RESONATE-17

Unfit Patients (no del17p, TP53 mutated, age ≥ 65)

mIGHV
Chlorambucil + obinutuzumab (Chlb+Obin) (funded)
Ibrutinib (not funded)
• Supported by ALLIANCE
Acalabrutinib (not funded)
• Supported by ELEVATE-TN

uIGHV
Ibrutinib (funded)
• Supported by ALLIANCE and RESONATE-2
Acalabrutinib (not funded)
• Supported by ELEVATE-TN

Key Study Highlights

ALLIANCE
Ibrutinib monotherapy and ibrutinib + rituximab (IR) demonstrated a PFS advantage over BR. The addition of rituximab to ibrutinib did not improve PFS over ibrutinib alone.

ELEVATE-TN
ELEVATE-TN demonstrated an advantage of acalabrutinib with or without obinutuzumab over chlorambucil with obinutuzumab. ELEVATE-TN also demonstrated a benefit with the addition of obinutuzumab (post-hoc analysis) - an antibody can potentially increase effectiveness when combined with a Bruton’s tyrosine kinase (BTK) inhibitor (BTKi).

Additional Trial/Combination to Watch For

CLL
CLL suggests that Ven+Obin offers a PFS and undetectable MRD (uMRD) advantage versus Chlb+Obin. This one-year regimen combines the time-limited aspect of chemoimmunotherapy (CIT) with novel targeted treatment. This treatment is not yet approved by Health Canada and long term follow-up is needed. In the absence of direct comparisons with the current standard, funding of alternative novel agent regimens in Canada will be challenging (in this setting).
Relapsed / Refractory CLL

Post-Chemoimmunotherapy (CIT)

Ibrutinib (funded)
- Supported by RESONATE

Venetoclax + rituximab (Ven R) (not funded)
- Supported by MURANO

Idelalisib + rituximab (funded, unless progressed on ibrutinib in R/R)

Study Highlights

**RESONATE**

RESONATE compared ibrutinib versus ofatumumab in R/R CLL patients and demonstrated an advantage for ibrutinib. After 6 years of follow-up, results from a mature analysis demonstrate a significant and sustained PFS and depth of response advantage for ibrutinib. Median PFS of 44 months for ibrutinib versus 8 months for ofatumumab (consistent across all subgroups). The median PFS had not yet been reached in patients who received ibrutinib in second line.

**MURANO**

MURANO (Ven R versus BR) establishes Ven R as a standard treatment option for R/R CLL and demonstrated a sustained OS and PFS benefit with time-limited treatment. The toxicity profile is favourable and TLS risk is mitigated with ramp-up and appropriate monitoring and (where necessary) hospitalization. Funding for Ven R is anticipated soon and may provide an alternative option to indefinite ibrutinib monotherapy.

Ibrutinib Failure

- Venetoclax (not funded)
- Idelalisib + rituximab (intolerance only)

After 6 years of follow-up, results from a mature analysis (RESONATE) demonstrate a significant and sustained PFS and depth of response advantage for ibrutinib.

Page 03
Sequencing of Ibrutinib and Venetoclax

- Both sequencing strategies (ibrutinib before venetoclax or venetoclax followed by ibrutinib) have demonstrated efficacy, therefore sequencing decisions are impacted by comfort and experience. However at this time there is more study evidence demonstrating patient response when venetoclax is used after ibrutinib.

Treatment Duration

- There are a subset of patients in which finite duration may be the preferred approach, but high-risk patients require continuous therapy.
- Treatment decisions are linked to access in Canada, and will impact physician and patient preferences in some cases.
- From a payer perspective there are benefits to limited duration therapies.
- Long-term, there will likely be a role for both strategies (finite and continuous) in Canada.

The Utility of Minimal Residual Disease (MRD)

- Although Canadian clinicians have been aware of the value of MRD testing for over 10 years, access to MRD testing in Ontario is limited.
- MRD status is prognostic, however it is not utilized in routine practice and does not currently influence treatment decisions.
- If ibrutinib + venetoclax (I+V) combination therapy is approved (investigated in CAPTIVATE), then MRD testing will take on new utility, as it can guide treatment discontinuation.

Novel Combination for First-line CLL (Ibrutinib + Venetoclax)

- I+V represents an all-oral, once-daily, chemotherapy-free regimen that provides high rates of undetectable MRD in peripheral blood (75%) and bone marrow (72%), in first-line treatment of CLL.
- Clinical results of the CAPTIVATE study validate the synergism of the combination seen in preclinical studies with highly concordant results (93%) for undetectable MRD between peripheral blood and bone marrow.
- Substantial reduction in venetoclax-related TLS risk after ibrutinib lead-in, with 90% of patients with baseline high TLS risk downgraded to lower risk categories.
- A favorable safety profile with ibrutinib + venetoclax was demonstrated with a low rate of discontinuation (5%) due to AEs - 90% of patients completed 12 cycles of combination therapy.
Available Now!

The CARE™ Global Interview Series

Issues of the CARE™ Global Interview series, featuring hematology leaders from Italy, England and the USA are available now.

CARE™ WHU 2020 Meeting Slides

Though nothing beats attending a CARE™ event, the complete presentations from WHU 2020, as delivered by members of the CARE™ Faculty, are available on the CARE™ website. CARE™ Guidance material is augmented by reviewing recent education content from the CARE™ Faculty - we encourage you to visit the CARE™ website for additional context and insights.

CARE™ Localized Modules

The CARE™ Faculty has produced general (non-regional focused) medical education slide decks on hematological topics in 2020. The CARE™ Localized Slide Decks are available on request. Contact CARE™ through the website to request one or more Localized Modules.

Coming Soon!

CARE™ CLL Patient Case Review and Publication

A CARE™ CLL Patient Case Review, informed by CARE™ Programming at WHU 2020 and led by Dr. Peter Anglin (Stronach Regional Cancer Centre, CARE™ Hematology Faculty Lead) will be available soon.

CARE™ Retrospective Reviews

2020 marks 15 years of CARE™! To capitalize on years of experience, and to use the past to help make projections for the future, CARE™ will be creating a series of retrospective reviews in various categories.


