CLL CANADA LLC CANADA

eBulletin
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CLL Canada UPDATE - ISSUE 27

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1. The Way Ahead as COVID Lingers On

A Word from the CLL Canada Board Chair

Sadly, I think the world has moved on and we need to teach our community self-protection and not expect society at large to act in our interest.

The consensus opinion at a recent international CLL Advocates Network meeting.

In 2022, the CLL Advocates Network (CLLAN) devoted considerable effort to developing and launching a vigorous campaign to advocate for better protection of immunocompromised blood cancer patients from COVID-19. CLL Canada is one of the 45 patient groups that make up CLLAN.

Less than a year later, a follow-up meeting of 19 CLL patient advocates from 14 countries agreed that "t*he world has moved on*". Asking others to take proactive measures on our behalf is no longer a viable strategy. We need to rethink our approach.

A consensus emerged that the way forward is to help people with CLL re-engage with the world. The revised CLLAN campaign should aim to provide patients with the tools to make informed and wise decisions about the risks they face and the

level of protection they need. The focus should be on providing information and advocating for supportive policies, such as the ready availability of antiviral medications such as Paxlovid.

So where are we now?

CLL Canada took an approach similar in the August 2021 special edition of our eBulletin, entitled *On the End of COVID Restrictions: the CLL Patient's Dilemma*.

The eBulletin began by taking a closer look at the data on mortality, hospitalizations and vaccine effectiveness in CLL patients. It then discussed how people with CLL could manage their risk and live with uncertainty.

Since then, we learned that:

- Morbidity and mortality have fallen significantly in CLL patients and blood cancer patients in general.[1]
- The CLL patients most at risk are those over 70 who have one or more serious comorbidities (e.g., dementia, other malignant diseases, diabetes, cardiac and pulmonary comorbidities)[2].
- The level of the virus in wastewater (sewage) is at a relatively low level in most of the sites measured, with levels decreasing (28% of the sites) or stable (42% of the sites)[3]. The data for this important indicator can be found on the Government of Canada website here.
- The more doses of anti-COVID vaccines a CLL patient has received beyond two doses, the more chance that they will seroconvert, that is, they will produce antibodies that will offer protection from COVID[4].
- Paxlovid has proven to be an effective treatment if taken within 5 days of the appearance of COVID symptoms. Interactions with CLL drugs (BTKi and BCL2) are a concern but can be managed[5].

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[1] The Outcomes of Covid-19 in Patients with CLL during the Omicron Sub-Variants Surge, Y. Bronstein et al, Blood (2022) 140 (Supplement 1): 7023–7024. https://doi.org/10.1182/blood-2022-158757

[2]Patients with CLL have a lower risk of death from COVID-19 in the Omicron era, Niemann,C., et al, Blood, Volume 140, Issue 5, 2022, Pages 445-450, https://doi.org/10.1182/blood.2022016147

[3]COVID-19 wastewater surveillance dashboard, Government of Canada website, consulted March 26, 2023, https://health-infobase.canada.ca/covid-19/wastewater/

[4] Multiple COVID-19 vaccine doses in CLL and MBL improve immune responses with progressive and high seroconversion, Shen, Y et al. .*Blood* (2022) 140 (25): 2709–2721 https://doi.org/10.1182/blood.2022017814

- A study has shown that it's use is associated with a lower risk of long COVID (post–COVID-19 condition)[6].
- Another indicator, which may or may not be significant, is that we have not heard about new variants since XBB.1.5 appeared back in December. It is often the appearance of a new variant that sparks a fresh wave of infections.

In summary, the available data indicates that the risk to people with CLL is the lowest it has been since the beginning of the pandemic. One thing that is unchanged is that those over 70 with other illnesses (comorbidities) are at greatest risk. For more detailed information, follow the web links in the footnotes.

However, each of us must make our own decision on the pace with which to re-engage with the world. We must balance the risk to our physical health with the very real benefits that come with re-engaging with the world: to our mental health and our enjoyment of life, to our family and to our friends.

The last two sections of the CLL Canada August 2021 eBulletin dealt with this very topic. How do we manage the unknown? How do we live with uncertainty? There are no hard-and-fast answers. We refer the reader to that discussion, here.

We will leave the last word to Dr. Brian Koffman, founder of the CLL Society in the United States, who recently wrote:

> *"I remind you of one of my most important commandments on how to cope with CLL/SLL that has served me well from the beginning of my journey:*
>
> ***You may need to make difficult decisions with imperfect knowledge and contradictory advice.***
>
> *Did any of us really think that SARS-CoV-2 would change that imperative?*
>
> *Take some deep breaths, stay informed, examine all the options, and make the best choices based on the present data. Then recorrect as needed as new information becomes available."*

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[5] COVID-19: Dr. Sameer Parikh on Drug Interactions Between Paxlovid and CLL/SLL Drugs, https://cllsociety.org/2022/01/covid-19-dr-sameer-parikh-on-drug-interactions-between-paxlovid-and-cll-sll-drugs/

[6] Association of Treatment With Nirmatrelvir and the Risk of Post–COVID-19 Condition, Y. Xie et al, JAMA Intern Med. Published online March 23, 2023 10.1001/jamainternmed.2023.0743

We hope that you will find our eBulletin a useful benefit from membership in a club that none of us wanted to join. Send your comments and suggestions to cllcanada.org@gmail.com

Please note that the information in this eBulletin was current as of the date it was published. In science and medicine, information is constantly changing and may become out-of-date as new data emerge.

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2. Additional COVID-19 Booster Recommended in the Spring of 2023

For individuals at high risk of severe illness due to COVID-19

On March 3, 2023, the National Advisory Committee on Immunization (NACI) published guidelines based on the 'best current available scientific knowledge recommending an additional booster be offered in the spring of 2023 for those who are at high risk of severe illness due to COVID-19.

This recommendation applies to CLL patients, more specifically, those who are moderately or severely compromised because of these conditions:

- Immunocompromised due to solid tumour or hematological malignancies (i.e., blood cancers) or treatments for these conditions
- Hematopoietic stem cell transplant (within two years of transplantation or taking immunosuppression therapy)
- Immunocompromised due to chimeric antigen receptor (CAR) T cell therapy targeting lymphocytes.

The recommended interval from the last COVID-19 vaccine dose or the last SARS-CoV-2 infection is 6 months or more, if applicable (whichever is longer).

Check here for additional information.

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3. CLLAN Webinars Take an In-Depth Look at CLL Treatments

In the last decade, the treatment horizon for CLL patients has dramatically changed, and there are exciting new research avenues being explored. Individualized therapy is now a reality, and patients and doctors are now armed with more options to discuss and choose the best treatment path.

The following are summaries of two recent webinars hosted by the CLL Advocates Network, of which CLL Canada is a member. The first provides timely and relevant information on treatments for relapsed-refractory CLL. The second covers advances in the development of highly effective BTK inhibitors as frontline therapy.

The first*, CLL Treatment in the Relapsed-Refractory Setting and Promising Therapeutic Approaches to Fulfil Unmet Needs,* is a one-hour presentation by Dr. Talha Munir, with comments from patient advocates Dr. Brian Koffman and Lelia Duley. They share complex information in an easy-to-understand way and highlight how the landscape for treating relapsed–refractory CLL is rapidly changing and what that means for CLL patients. A full summary of the webinar topics, including the link to the video recording, can be found here.

The second one-hour webinar, *How Are Advances in Brutons-Tyrosine-Kinase (BTK)Targeted Therapies Continuing to Change How CLL is Treated?,* provides a deeper dive into the world of BTK inhibitors as frontline therapy. UK professors Chris Pepper and Chris Fegan do an excellent job of sharing complex scientific information in a way that broadens our understanding of the various BTK inhibitors that are currently available and those that are under development. A full summary of topics covered in the webinar can be found here, along with the video recording.

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4. Updated Canadian CLL First Line Treatment Guideline

A useful resource for patients

CLL is a complex disease. It is not easy for a CLL patient to sort out which treatment is best for his or her variety of the disease. A newly updated Canadian clinical guideline provides a helpful summary of the treatment options for the different variations of CLL.

In 2022 Lymphoma Canada coordinated the update of the 2018 Canadian clinical practice guideline, working closely with a panel of CLL experts from across Canada. An evidence-based approach was used through compiling and analyzing articles and publications that fit identified criteria.

While doctors are the primary audience for the guideline, it is an informative read for CLL patients as well. It provides a basis for discussions with doctors as the time for treatment nears, and it promotes a consistent approach to treatment across Canada while acknowledging there are differences in access and funding across the country. The full paper with recommended guidelines can be accessed here.

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4. CLL Canada News

CLL Live Survey

Many thanks to all the members who completed the CLL Live survey. It is heartening to see that 52% of respondents indicated they were likely or very likely to attend a CLL Live in 2024.

The results of the survey will be very helpful to the CLL Canada Board of Directors at its June meeting when it decides whether or not to go ahead with a CLL live in 2024.

Health Technology Assessment Submissions

With our partners Lymphoma Canada, we have been busy preparing submissions of the patient perspective to agencies charged with evaluating new treatments, INESSS in Quebec and CADTH for the other provinces. In February, we submitted a brief supporting the use of Zanubrutinib. A patient survey to enable us to prepare a submission on the combination of Ibrutnib and Venetoclax for first-line treatment is currently available here.

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5. Management of Relapsed/Refractory CLL

Assessing the options for treating relapsed/refractory CLL treatment

While many people have benefitted from treatments that can put CLL and some of its various symptoms into remission, there is unfortunately no known cure. When remission ends and CLL returns, it is called relapsed/refractory CLL.

The development of many new oral CLL treatments during the past 10 years has created new challenges when it comes to choosing the best sequence of therapy. Hematologist Jennifer A. Woyach discusses these challenges in her paper "Management of relapsed/refractory Chronic Lymphocytic Leukemia" published last year in the American Journal of Hematology. Dr. Woyach reviews each of the treatments currently being used for relapsed/refractory CLL. Examining current research, she concludes that a patient's first treatment type is the most important consideration when choosing a second one. She then provides a noteworthy decision tree of therapeutic options for relapsed/refractory CLL.

Dr. Woyach's intended audience is other doctors. Even so, the information can be helpful to patients anticipating discussing second-line treatment options with their doctors. The full article can be found here.

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6. Turning a CLL Diagnosis into Music

When people first receive a cancer diagnosis, there are many ways we deal with the myriad of feelings this brings on. In 2022 singer-songwriter Dennis Kalichuk was diagnosed with CLL, which inspired him to write a song called *When Will it be Okay*, released in March of this year by Jumbo Train. You can see the video of the performance here.

7. ASH Annual Meeting Highlights Progress in CLL Treatment

The American Society of Hematology's (ASH) annual meeting is the most important event in the field of blood cancers, attended by hematologists from around the world. Thanks to the magic of the Internet, CLL Canada co-founder and honorary board member Deborah Baker was able to attend the most recent meeting from the comfort of her own home, though the actual conference was held in New Orleans, Louisiana from Dec 10-13, 2022 with 30,000 attendees.

After many years of lobbying, representatives of patient advocacy groups are welcomed at no charge, in person or virtually, in what used to be a doctor only meeting. The following are highlights from the 2022 meeting.

CLL therapy has undergone a revolution in the last decade with the availability of highly effective targeted therapies. The options continue to expand with next generation inhibitors and combination therapy. The variety of available options can be confusing and their optimal use over a patient's entire disease course is still often unclear.

The Most Common Treatments for CLL

Treatment type	Commercial Names	Medical Name	Time limited or continuous	Form	Notes
Chemo-immunotherapy	Fludarabine, Cyclophosphamide & Rituximab (FCR)		Time limited	Intravenous in a hospital or clinic	Only for patients with mutated IGHV who are fit and under 65.
	Bendamustine & Rituximab (BR)		Time limited		
Covalent BTKi	Imbruvica	Ibrutinib	Continuous	Pill	First generation
	Calquence	Acalabrutinib	Continuous	Pill	Second generation
	Brukinsa	Zanabrutinib	Continuous	Pill	Second Generation
BCL2i	Venclexta	Venetoclax	Time limited	Pill	Often given with an anti- CD20
Anti-CD20	Rituxan	Rituximab	Time Limited	Intravenous in a hospital or clinic	Often given with a targeted therapy
	Gazyva	Obinutuzumab	Time Limited		

The options for initial CLL therapy still include chemo-immunotherapy (CIT) in 60% of patients worldwide and 33% of USA patients. Flatiron Health database analysis from 280 US cancer clinics shows 46% (N=3654) of CLL patients received targeted

continuous therapy – Bruton's Tyrosine Inhibitor (BTKi) with or without an anti-CD-20 inhibitor such as rituximab (Rituxan)or Obinutuzumab (Gazyva) or time-limited therapy with a BCL2i (B-cell leukemia/lymphoma 2 protein) such as Venetoclax (Venetoclax) with or without an anti-CD-20 inhibitor. A major challenge is clarifying 'optimal candidates' for time-limited vs continuous therapy as well as toxicity/treatment discontinuation in continuous BTKi therapy.

Second generation BTKi include Acalabrutinib and Zanabrutinib. Along with Ibrutinib, these are considered covalent BTKi. Acalabrutinib and Zanabrutinib have a better adverse effect (AE) profile with less atrial fibrillation and hypertension than Ibrutinib and are also preferred for patients with del(17p)/TP53 mutations.

Recent trials of both first line and subsequent treatments include doublet therapy with BTKi and Venetoclax-based combinations, as well as triplet therapy using a BTKi and Venetoclax with an anti-CD-20 inhibitor. The combination of Ibrutinib and Venetoclax achieved durable responses, clinically meaningful progression-free survival, and treatment-free remissions; and it has been approved by the European Medicines Agency. Combinations appear to be highly effective, but safety may be a consideration especially in older patients.

More patients are developing disease progression after treatment with both BTK inhibitors and Venetoclax (also called double refractory CLL), which represents a new significant unmet need. Third generation non-covalent BTKi, including Pirtobrutinib (Jaypirka) and Nemtabrutinib, are now in Phase III clinical trials. Clinical trials to date have shown them to be effective treatments for relapsed patients. CAR-T therapy can also be considered in these situations.

The next wave of CLL treatments is under development, including 4^{TH} generation BTKi, bispecific antibodies that bind on two different targets and treatments that degrade the BTK protein instead of blocking it as BTKi drugs do now.

Some treatments on the horizon to watch for include:

- MS-553, a potent, highly selective, oral, non-covalent inhibitor of protein kinase C (PKC) β, an essential signalling molecule immediately downstream of BTK and PLCγ2 in the BCR pathway. As PKCβ is downstream of both BTK and PLCγ2, inhibition of PKCβ has the potential to treat acquired resistance mutations from either protein.
- BGB-11417 monotherapy, a highly selective Bcl-2 inhibitor with potency >10 times that of Venetoclax in biochemical assays.
- Lisaftoclax, a specific BCL-2 inhibitor, active in patients with Relapsed and Refractory CLL/SLL, including patients with del(17p) and progressive disease (PD) after BTKi therapy. Lisaftoclax is combined with Acalabrutinib or Rituximab in patients with CLL/SLL (NCT04215809).

- NX-2127, a first-in-class study of a BTK degrader, a novel small molecule that drives targeted BTK and IKZF3 degradation through ubiquitination and proteasomal degradation. This BTK degradation and immunomodulatory activity represents a novel mechanism of action and may overcome resistance to currently available novel agents including covalent BTKi and non-covalent BTKi, addressing the unmet medical needs of patients whose disease is refractory to any BTKi (including ncBTKi) and a BCL2 inhibitor.
- The TRANSCEND-CLL TRIAL with CAR-T cell therapy is studying lisocabtagenemaraleucel (liso-cel) in heavily pretreated patients with relapsed/refractory CLL/SLL including those who have received prior ibrutinib and/or Venetoclax. Barriers to CAR-T therapy include slow approval process by payers, slow intake process at CAR-T center, patient deterioration prior to CAR-T, lack of communication from CAR-T center, and inability to manufacture the product.
- Richter's syndrome, the transformation of CLL to an aggressive lymphoma, can affect about 10% of CLL patients and remains a major clinical challenge; but new therapies including CAR-T are helping to improve outcomes.

This meeting is an opportunity for hematology professionals to share their research including updates on trials and information about new clinical trials for malignant and non-malignant conditions. It should be noted that the information covered is mainly for developed countries, as developing countries have very few clinical trials and still rely mainly on chemoimmunotherapy (CIT) for CLL, most likely because of the high cost of targeted therapies. Patient choice has become more of a factor when determining treatment in developed countries, and clinical trials give patients more choice.

For more information:

https://www.patientpower.info/chronic-lymphocytic-leukemia/2022-ash-conference-report-deep-dive-into-cll

https://www.vjhemonc.com/subject/chronic-lymphocytic-leukemia/

https://www.vjhemonc.com/event/post-ash-2022-lymphoma-cll/

https://www.clinicaloptions.com/oncology/programs/2022/cll-heme-2022

https://www.onclive.com/clinical/cll

https://www.onclive.com/conference/ash