CLL CANADA LLC CANADA

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CLL Canada UPDATE - ISSUE 26

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A Word from the CLL Canada Board Chair

Living with CLL requires us to play the long game. Since treatment only controls the disease rather than cures it, our current treatment decisions need to consider the options that will be available to us if the disease comes back. Like a good chess player, we need to think a few moves ahead of where we are now.

The good news is that our options are expanding. Two classes of targeted treatments that expand our options have become available in Canada: BTK inhibitors Ibrutinib, Acalabrutinib, Zanubrutinib (the latter is only available for CLL through the Special Access Program); as well BCL2 inhibitor Venetoclax. Clinical trials of combinations of two or three treatments are ongoing and new treatments are in development.

In this eBulletin we look at the current treatment landscape from several perspectives: historical; medical; scientific; regulatory; and that of the patient, who is now having to make choices about treatment.

We hope that you will find our eBulletin informative. Send your comments and suggestions to cllcanada.org@gmail.com

Please note that in science and medicine, information is constantly changing and may become out-of-date as new data emerge. The purpose

of this eBulletin is to inform, it is not to provide medical advice. Patients should consult with their health care practitioner(s) before acting on the information in this eBulletin.

A Ten-Year Retrospective on CLL Treatments

The development of targeted treatments over the last decade has completely changed the CLL treatment landscape. These treatments which target specific proteins are more effective and better tolerated by patients than chemotherapy, which was previously the mainstay of CLL treatment. A historical overview of the advances that have greatly improved the outlook for people with CLL can be found here.

Challenges and Changes with Targeted Options in CLL

In this YouTube video, two well-known CLL specialists, Dr. Nicole Lamanna and Dr. Deoborah Stephens, review the studies on the effectiveness and side effects of BTK inhibitors and Venetoclax. They also discuss the sequencing and combination of treatments as well as some of the new drugs presently in clinical trials. They finish with a discussion of case studies of patients with different profiles (age, comorbidities, etc.). This video is rich in information yet not so technical as to be difficult to understand, making it worth investing the hour required to view it.

Can Venetoclax Treatment be Repeated?

As we all know, relapse from treatment is not uncommon in CLL. Running out of options is a concern to those of us who require a succession of different treatments to keep our CLL at bay. But what if we could repeat the same treatment one or more times?

A recent study of CLL patients who relapsed after their initial Venetoclax treatment found encouraging evidence of a good response to a second Venetoclax treatment.

The overall rate of response (ORR) after the re-treatment with Venetoclax was 79.5% compared to 95% after the initial Venetoclax treatment. After two years, CLL was not progressing in half of the 46 patients in the study.

There are several limitations to this study including the small sample size and that all but four participants had been through several other treatments, making their CLL more resistant. Although the authors point out that more studies are needed, this study indicates that retreatment with Venetoclax may be a viable option for some people with CLL. A summary of the study was posted on the CLL Forum of Health Unlocked.

CLL Canada News

NACI Broadens the Definition of who is Immunocompromised

During the COVID-19 pandemic, people with compromised immune systems were given access to preventative and anti-viral treatments because they were at higher risk of developing severe illness. Cancer patients were included, but only if they were under treatment, effectively excluding many people with CLL who are also immunocompromised in watch-and-wait as well as after treatment is completed.

CLL Canada teamed up with Lymphoma Canada and the Leukemia and Lymphoma Society of Canada to write to the National Advisory Committee on Immunization (NACI) asking them to broaden their definition of immunocompromised to include CLL and lymphoma patients at all stages of their disease.

We were gratified to find out last June that the new definition included people who are "*Immunocompromised due to solid tumour or hematologic malignancies or treatments for these conditions".* We are hoping that provincial ministries of health will take heed of this new definition and modify their own definitions appropriately.

CLL Information and Resource Centre

CLL Canada marked World CLL day on September 1 with the launch of the CLL Information and Resource Centre on our website. This new page is designed to help patients find credible, timely information on the Internet about CLL and the challenges of living with it.

World CLL Day

CLL Canada's World CLL Day campaign focused on providing information and to patients about CLL and its treatments. We began by launching the CLL Information and Resource Centre on our website to enable patients to find credible, timely information on the Internet about CLL and the challenges of living with it.

We promoted the new web page to health professionals, primarily doctors and nurses, so that they might inform patients they deal with daily of this valuable information resource. Thanks to the sponsorship of AbbVie, we were able to work with a communications firm to publish articles for two medical publications as well as some targeted advertisements.

CLL Canada in the Media

CLL Canada Board members have participated in articles appearing on the Healthing.ca website

Mekki MacAulay was featured in an article on the challenges of being immunocompromised during the COVID 19 pandemic. Board Chair Raymond Vles recounted his CLL journey in an article on CLL.

In August of this year, an op-ed article on the theme of being immunocompromised during the pandemic was published in the opinion section La Presse by CLL Canada Board Chair Raymond Vles. The original article is in French, a Google translate version in English is here.

Canadian CLL Research Meeting

Board Chair Raymond Vles was invited to speak at the Canadian CLL Research Meeting in early September. Our key message to this gathering of Canadian and American clinicians and researchers was that patients who are well informed about CLL have better outcomes. Clinicians in particular could help patients become better informed by referring them to the CLL Information and Resource Centre on the CLL Canada website.

CLL Canada is Looking for Board Members

We have some openings on our Board of Directors for CLL patients and caregivers from across Canada. We are an all-volunteer organization, so Board members play an active role in our activities. You can find information about CLL Canada and the role of the Board on our website, here.

Should you be interested or want more information before deciding to apply, please send us an email cllcanada.org@gmail.com

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Once Again, Federal Regulations Threaten New Drug Availability

Two years ago, we published a special edition of our eBulletin criticizing the pending amendments to the Federal Government's *Patented Medicines Regulations*. The objective of the amended regulations was to lower the prices of drugs in Canada.

While lower prices are always welcome, patient groups across the country were worried that these new regulations would hinder the timely introduction of innovative new medicines to Canada.

In 2021, the courts ruled against the amended regulations as they were then conceived, following a challenge by the pharmaceutical industry.

Unfortunately, that was not the end of the issue. A new version of the regulations was recently released for consultation by the federal agency administering the regulations, the Patented Medicine Prices Review Board.

Once again Canadian patient organizations are concerned that innovative new therapies will become available in Canada much later than elsewhere, if at all.

While drug companies can go to other countries to sell their drugs, most Canadians are not able to travel to the United States or elsewhere to receive treatment.

We will be following this issue and collaborating with other patient organizations to make our concerns known to the federal government.

Treatment Combination Effective Despite Failure as Monotherapy

A small study of 13 patients whose CLL has returned after numerous treatments found that the taking Ibrutinib or Acalabrutinib together with Venetoclax can bring CLL back under control. These patients had previously taken these drugs individually as monotherapy without achieving long lasting remissions.

Despite the previous use and despite having many risk factors, the combination gave 9 patients a partial response and stabilized the disease in 2 patients. The CLL progressed in the 2 remaining patients.

It is not known why the combination works in patients who have had their CLL come back when they took both drugs individually. Nonetheless, it opens another option for CLL patients. It is not clear, however, whether this treatment will be funded by the provincial governments who decide which drugs they will pay for in their jurisdiction.

Is BTKi or BCL2i preferable as first novel therapy in patients with CLL?

By Spencer B. Gibson, Ph.D. and Raymond Vles

It's been said that every solution brings with it new problems. Now that targeted treatments of CLL have largely replaced chemotherapy, patients are now faced with the problem of choosing between two treatments. In the absence of head-to-head studies between BTKi drugs (Ibrutinib, Acalaburtinib, Zanubrutinib) and BCL2i drugs (Venetoclax), how are we to know which of these is the best?

This question was debated in two compelling articles in the journal BLOOD where two prominent scientists Dr. John Seymour, University of Melbourne, and Dr. Susan O'Brien, UC Irvine Medical Center, took opposite positions on which frontline therapy is best for CLL patients. We will summarize their arguments and hopefully make it easier to understand what treatment is best for individual CLL patients.

Both targeted therapies are effective at killing CLL cells but have different mechanisms of action that could determine which CLL patients will benefit the most.

BTKi drugs disrupt a process necessary to the survival of CLL cells by inhibiting an enzyme called BTK. As a result, CLL cells leave lymph nodes and bone marrow for the bloodstream where they die like normal cells. However, if the drug is stopped, the process resumes enabling the CLL cells to survive. For this reason, BTKi drugs need to be taken indefinitely.

BCL2i drugs work differently. They bind to a protein called BCL-2, preventing the protein from fulfilling its usual function of prolonging the life of CLL cells, which

then die off to the point where there are so few as to be undetectable. This is the reason that treatment with BCL2i drugs can be time limited rather than continuous like the BTKi. However, BCL2i drugs are usually given with a monoclonal antibody such as Rituximab or Obinutuzumab, requiring visits to a hospital or infusion clinic.

The case for BTKi as frontline treatment is strong and has the most evidence supporting its use, mainly because as the drug has been in the clinical setting longer than BCL2i. BTKi treatment allows patients to take one drug and have long-term remissions with greater than 90% of patients responding to treatment in clinical trials.

Being able to take a pill at home also has the benefits of avoiding trips to the hospital or infusions centres to get antibody therapy. This has been particularly important during the COVID19 pandemic.

BTKi drugs are effective even in patients with bad prognostic makers: 17p or TP53 deletions and unmutated IgHV. Clinical data indicate that patients respond similarly to BTKi whether or not they have these markers. In contrast, BCL2i effectiveness in 17p or TP53 deleted patients has not been determined, making BTKi the preferred treatment in these patients.

Despite BTKi's advantages, there are several concerns about its use. The side effects of BTKi can temper its use, in particular in patients with a history of heart problems or bleeding disorders. Nonetheless, young patients that can tolerate the side effects or older patients with high-risk factors are more likely to receive frontline BTKi because the benefit of BTKi outweigh the potential side effects. In clinical trials newer BTKi such as acalabrutinib showed similar effectiveness to ibrutinib while causing fewer heart problem and bleeding in patients.

The fact that a patient will be taking BTKi for many years is as concern. It increases the chances the CLL will mutate to become drug resistant and more aggressive. In addition, the cost to the health care system is significant. We hope that as more BTKi drugs come to market, competition will drive the cost down, but this does not appear to be happening to date.

The case for BCL2i as frontline treatment is also compelling. So far, the only BCL2i approved for CLL treatment is Venetoclax in combination with anti-CD20 therapies (Rituximab or Obinutuzumab). Other BCL2i drugs are under development, but it is too early to say whether and when they will become available in Canada.

One major advantage of BCL2i therapy is it occurs over a limited time, reducing both the cost and the likelihood of developing resistance to the treatment.

This has two major implications: 1) re-treatment with BCL2i is possible should the CLL return after a first treatment, and 2) the ability to detect whether any CLL cells are left in the body, called the minimal residual disease, can provide early indication for the success of the treatment.

Venetoclax treatment requires more hospital visits than BTKi for monthly infusions of the anti-CD20 therapy usually given with the drug. Close monitoring of patients is required at the beginning of treatment lest the drug kill so many CLL cells as to overload the body's ability to cope, what is called tumour lysis syndrome. While this can be safely managed, some patients may have to be admitted to hospital.

It should be noted that most CLL patients seem to have trouble building an effective COVID antibody response after vaccination, and both BTKi and BCL2i therapies only make the response to vaccines worse.

In summary, BTKi or BCL2i therapies are both good choices for patients to achieve long-term disease-free survival. In the absence of head-to-head comparison trials and long-term follow-up on patients, the choice comes down to the preference of patients and their treatment objectives.

Does the patient prefer continuous or time-limited therapy? Does the patient have easy access to the hospital or clinic during working hours or do they have to travel, arrange childcare or take time off work? Does the patient have other health issues – comorbidities– that would make them more vulnerable to a particular side effect of one of the drugs? As we mentioned above, available data indicates that BTKi is more effective in patients with a 17p or TP53 deletion.

Irrespective of what frontline targeted therapy was used, if the disease returns there is evidence that using the other targeted therapy drug will be effective. This gives patients options if the initial therapy fails.

This is truly a new era in CLL therapy and CLL patients will be on the frontier of how targeted therapies will be used in cancer. As new BTKi are developed and as more clinical knowledge of BCL2i builds, it will be clearer what frontline treatment should be used in individual CLL patients. Until that time, both BTKi and BCL2i are effective choices that will supplant immunochemotherapy.

The original articles are part of a Point-Counterpoint feature in Blood Advance Journal called *Is BTKi or BCL2i preferable as first novel therapy in patients with CLL?* *The Case for BCL2i*, and *The Case for BTKi*.