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March 2, 2022

Dr. Anne Pham-Huy
Lead Physician, Primary Immunodeficiency Clinic
Children's Hospital of Eastern Ontario

RE: Urgent Need to Revise NACI's immunocompromised definition to include lymphoma and CLL regardless of treatment status

Dear Dr. Pham-Huy,

We have heard from many Canadians affected by lymphoma and chronic lymphocytic leukemia (CLL) who are very confused as to why they are not considered immunocompromised. For this reason, CLL Canada, Lymphoma Canada and The Leukemia and Lymphoma Society of Canada are urgently writing to you today.

On behalf of our community, we respectfully request that the National Advisory Committee on Immunization reconsider and revise its current definition of immunocompromised individuals so as to formally recognize patients suffering from lymphomas and chronic lymphocytic leukemia (CLL) as being immunocompromised, whether or not they are under treatment. The current recommendation[1] identifies certain groups as immunocompromised for the purposes of COVID-19 vaccination recommendations. Canadians with lymphoma and CLL are in this category of cancer patients, however the current recommendation only includes those who are receiving active treatment for their condition.

Treatment versus no Treatment

In the appendix to this letter, we present the evidence supporting our contention that lymphoma and CLL patients are immunocompromised before, during and after treatment. In summary, the research shows that:

- Hematologic patients experience more complications, morbidities and higher mortality rates when contracting the COVID-19 virus compared to the general population (references (H9 to H13)
- Lymphoma and CLL patients have an increased risk of serological non-response[6,8,10,11] and are therefore likely to receive less protection from vaccination than the general population, or none at all.

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- CLL and NHL patients who ended treatment more than 24 months before receiving their vaccine still showed reduced response rates (66.7% and 71.4% respectively) compared to healthy controls[11].
- Immune dysregulation is a cardinal feature of hematologic malignancies, including CLL at all stages of the disease, even when the disease is stable[2].
- As a cancer of immune cells, lymphoma perturbs immune networks, resulting in qualitative and quantitative dysfunction via a reduction in normal immune cells, accumulation of abnormal cells, and/or loss of normal communication between immune cells. (reference L2 and L3)

To exclude those who are not currently undergoing treatment seems to us an arbitrary decision which leaves those in watch and wait before treatment, a period which can last many years, as well as those who have completed treatment off the list of those who can receive the more expeditious COVID-19 vaccinations offered to other immunocompromised patients. Furthermore, it may exclude these patients from having access to anti-viral and monoclonal antibody treatments, since many provinces have adopted the NACI's definition of "immunocompromised" to determine which patients can receive these therapies if they are infected by COVID-19.

For Your Reconsideration

In conclusion, as hematologic patients were not tested on safety and vaccine efficacy in the initial vaccine clinical trials, evidence for understanding the impacts of the vaccine in these patient populations has only recently come to light. Therefore, it is not surprising that the immunocompromised definition that exists is not representative of all immunocompromised patients that require access to the vaccine and treatments.

We urge NACI to revise its current definition of who is immunocompromised to specifically mention lymphoma and CLL patients, whether they are under treatment, before treatment or after treatment. With provinces looking to NACI to guide their own definition for immunocompromised, this will allow lymphoma and CLL patients who are immunocompromised to gain priority access to the vaccines and necessary treatments sooner so that they can ensure they are protected from the virus that can prove fatal to them. As we hear from our patients:

> *"Advocacy groups need to talk about how their members are vulnerable... People need to know that for us this is not going away, and that the vaccine does not work in us the same way."*

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Now that COVID restrictions are being lifted across the country, community spread of the COVID virus is expected to increase, putting the immunocompromised at even greater risk. NACI must move quickly to revise its definition and encourage the provincial health ministries to follow suit so as to ensure that lymphoma and CLL patients who are not under treatment have the same priority access to vaccination and treatments as the rest of the immunocompromised population.

We therefore urge NACI to reconsider its existing definition and would be pleased to assist and provide guidance in any way that would facilitate our lymphoma and CLL patients getting access to the vaccine and other treatments sooner in accordance with their physician's approval.

Thank you for your consideration of this urgent request. Please email Indrek Koppel at indrek.koppel@lls.org should you wish to speak with us further.

Sincerely,

Indrek Koppel
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Appendix: Evidence from Research

The impact of the pandemic on the lymphoma and CLL population, as it related to the vaccines, mental and physical health, and access to treatment, can be found through the Lymphoma Canada COVID-19 Patient Experience Report[12].

Evidence Supporting the Inclusion of CLL Patients Regardless of Treatment Status in the Recommendation

CLL is a cancer of the immune system and as such those diagnosed with the immune dysfunction are immunocompromised, whether they are awaiting treatment, receiving treatment or are in remission following treatment.

> "*Immune dysregulation is a cardinal feature of chronic lymphocytic leukemia (CLL) from its early stage and worsens during clinical observation, even in absence of disease progression[2]*"

The consequence of this immune dysregulation can be fatal to CLL patients. Indeed, a study of 9,170 CLL patients in Denmark found that infections was the leading cause of mortality, with CLL itself as the second leading cause[3].

Consequently, CLL patients have a sub-optimal response to vaccination for COVID, as has been established by several studies.

> "*931 out of 1753 patients with chronic lymphocytic leukemia showed an antibody response, and the pooled response was 50% (95% CI, 43-57), with high heterogeneity (I^2=84%)[4].*"

Another study determined that the response rate in CLL patients receiving the mRNA vaccine was significantly reduced in comparison to sex and age-matched healthy controls (52% versus 100% respectively)[6]. Therefore, regardless of whether CLL patients are on active treatment or not, their response rate to the vaccine is substantially reduced due to the nature of their cancer.

Evidence Supporting the Inclusion of Lymphoma Patients Regardless of Treatment Status in the Recommendation

Lymphoma is a broad term for cancer of the cells of the lymphatic system, and is categorized into over 80 unique subtypes, each with their own clinical characteristics and treatment approaches. As the lymphatic system is an important component to the immune system, cancer of immune cells impairs the functioning of the immune system.

- *"Lymphoid malignancies such as lymphoma are particularly problematic as the transformation of these cells compromises host defense, and often these tumors evolve mechanisms to evade or escape immune surveillance(L1).*

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- *As a cancer of immune cells, lymphoma perturbs immune networks, resulting in qualitative and quantitative dysfunction via a reduction in normal immune cells, accumulation of abnormal cells, and/or loss of normal communication between immune cells (L2-L3).”*

Several published studies confirm that the lymphoma population are at increased risk of a reduced response to the vaccine. Patients that received two doses of the vaccine only showed a 51% seropositivity[7]. Further, lymphoma subtype can also play a difference in the vaccine response rate, whereby patients with more aggressive non-Hodgkin lymphomas have a weaker response than those with indolent non-Hodgkin lymphomas, those with Hodgkin lymphoma having the better response. However, regardless of subtype, responses rates are significantly worse than healthy controls[7,8].

> *“ The antibody response to the COVID-19 vaccine was achieved in 49% of patients with non-Hodgkin Lymphoma compared to 98.5% of age-compatible health controls[9]”.*

The results of numerous studies highlight that amongst hematologic patients, CLL and lymphoma patient are at a significant disadvantage regarding their response rate to the vaccine, and this is only worsened with treatment.

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