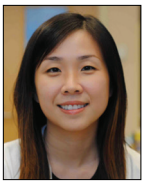
CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Preventing Infectious Complications in Chronic Lymphocytic Leukemia



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H&O What causes the elevated risk of infections in patients with chronic lymphocytic leukemia (CLL)?

CS Immunologic defects in patients with CLL are caused by the disease itself and by treatments that suppress the immune system. Patients with advanced CLL tend to develop hypogammaglobulinemia, which is associated with an increased risk of infection. CLL can also interfere with T-cell function and differentiation and complement that opsonizes encapsulated bacteria.

H&O Which patients are at especially high risk?

CS Patients with the most advanced disease tend to have the worst immune dysfunction. For example, we follow the level of immunoglobulin G (IgG) in clinical practice to monitor hypogammaglobulinemia; patients with the lowest IgG levels tend to be at the highest risk for infections. Moreover, the treatment itself can place patients at higher risk, depending on what specific type of treatment they are on. Back when patients were receiving chemoimmunotherapy, for example, cases of *Pneumocystis* pneumonia were reported. Anti-CD20 monoclonal antibodies—rituximab and now obinutuzumab (Gazyva, Genentech)—can lead to hepatitis B reactivation.

H&O Could you provide more detail about the types of infections that can occur in CLL?

CS The respiratory tract is the most common site of infections for patients with CLL, which can present as pneumonia, recurrent or chronic sinusitis, or bronchiectasis. Bacterial infections may occur in the genitourinary tract (urinary tract infections) and the skin (cellulitis). In addition, there is a risk of herpesvirus infections and reactivation, such as shingles from the herpes zoster virus.

Treatment can also lead to its own spectrum of infections. Most treatments increase the risk of herpesvirus reactivation further than CLL alone. One of the standard treatments for CLL is Bruton tyrosine kinase (BTK) inhibitors. Rare cases of invasive fungal infections have been reported in heavily pretreated patients who receive the BTK inhibitor ibrutinib (Imbruvica, Pharmacyclics/Janssen). Cases of *Pneumocystis* pneumonia also have occurred with ibrutinib, although the presentation tends to be less severe than what we see with chemoimmunotherapy or in patients with HIV. As I mentioned earlier, anti-CD20 monoclonal antibodies can lead to hepatitis B reactivation, so we always use serology to screen for prior hepatitis B infection before using them. Venetoclax-based therapies are often associated with a low neutrophil count, but fortunately, neutropenic fever is relatively uncommon among patients who receive growth factor support.

H&O How does having CLL affect vaccine recommendations?

CS Patients who have CLL fall under the immunocompromised designation in the Centers for Disease Control adult immunization schedule.[1] These are the guidelines that I follow in my practice. For this upcoming cold season, I have been recommending the COVID booster vaccine and the flu shot to my patients with CLL. Two respiratory syncytial virus (RSV) vaccines have received US Food and Drug Administration approval for patients

aged 60 years and older, and I advise an RSV vaccine for all my CLL patients older than 60 and some patients who are younger than 60, especially if they have underlying respiratory illness.

Vaccines are one of our most cost-effective measures for preventing infection. The key for CLL patients is to immunize early, when their immune system is best able to mount a good response. The active surveillance period is an ideal time to make sure that patients are up to date on all recommended vaccines.

A final note regarding vaccines is that live vaccines are contraindicated for patients with CLL. Even though live vaccines have been attenuated, they carry a risk of replication and potential infection in an immunocompromised host. For example, there were some cases of disseminated shingles with the previous iteration of the zoster vaccine, which was a live, attenuated version.

H&O What additional preventive strategies can be used against infection?

CS We have additional strategies for preventing infections, such as immunoglobulin replacement with intravenous immunoglobulin (IVIG) for patients with hypogammaglobulinemia. This approach is considered for patients with an IgG level of less than 4 g/L and with a history of bacterial infections. There is also a subcutaneous form of IgG replacement that is more commonly used in Canada and Europe.[2] This can be a good option for patients who do not wish to travel back and forth to an infusion clinic.

Another approach is the use of antimicrobial prophylaxis during treatment. For example, patients who have already had an episode of shingles can benefit from secondary antiviral prophylaxis. Patients who are at high risk for invasive fungal infections, such as aspergillosis, may benefit from the use of antifungals. I rarely use antibiotics to prevent bacterial infections, but sometimes they are appropriate for a patient who has prolonged neutropenia.

H&O What other considerations are there when choosing among different preventive strategies?

CS There are some special considerations when it comes to vaccines in patients who are on anti-CD20 monoclonal antibodies. Research has shown that treatment with these agents depletes the B cells and prevents patients from mounting an antibody response to vaccines, so I typically defer vaccines for at least 6 months after an infusion of rituximab or obinutuzumab. This gives patients the best chance of responding to the vaccine. Our group at the National Institutes of Health recently showed that treatment with a BTK inhibitor also can suppress vaccine responses.[3] This is hard to address because BTK inhibitor treatment is continuous and indefinite. We are currently conducting a randomized study in which patients either continue or briefly interrupt their treatment during the vaccine period to see if that could influence the response to the vaccine (NCT05170399).

H&O Are there any additional considerations when it comes to COVID infections?

CS Previously, there was a monoclonal antibody combination used to reduce the risk of COVID infection, but this is no longer authorized for use in the United States because in vitro assays showed that it is unlikely to be active against current variants. AstraZeneca is currently testing AZD3152, a different monoclonal antibody, against COVID (NCT05648110). I prescribe nirmatrelvir/ritonavir (Paxlovid, Pfizer) to reduce the severity of disease in CLL patients with COVID infections.

H&O What questions remain unanswered?

CS An elusive goal in CLL is to restore the immune system to its normal state.[4] This need became even more pressing with the onset of the COVID pandemic, which caused a lot of our patients to end up living isolated in a bubble for years. Most of our treatment studies in CLL are very disease-focused, with disease control as the study endpoint. I would love to see measurements of immune status incorporated into the design of studies. We know that both BTK inhibitors and venetoclax can reverse some of the immune deficits that occur with CLL, but others remain unchanged and may be long-lasting.

A group in Denmark is conducting a very interesting phase 2 trial that employs artificial intelligence (AI) to identify newly diagnosed patients with CLL who are at elevated risk of infection or early treatment (NCT03868722). These high-risk patients are being randomized to either a 3-month course of therapy with acalabrutinib (Calquence, AstraZeneca) and venetoclax or observation alone. The goal is to see whether treatment with CLL-directed therapy improves event-free survival in these patients. I think it represents progress to see a study looking at infections as a primary endpoint.

Disclosure

Dr Sun has received research funding from Genmab.

References

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4. Sun C, Wiestner A. Can immunocompetence be restored in chronic lymphocytic leukemia? *Hematol Oncol Clin North Am*. 2021;35(4):827-845.