Room for Improvement: Immunizations for Patients With Monoclonal B-Cell Lymphocytosis or Chronic Lymphocytic Leukemia

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Abstract: Infection is the cause of death in 30% to 50% of patients with chronic lymphocytic leukemia (CLL). A major strategy to decrease infection risk is vaccination. However, vaccine response rates in patients with CLL are typically insufficient. Recent studies have demonstrated that individuals with clinical monoclonal B-cell lymphocytosis (MBL), the precursor to CLL, also have an increased risk of infection and thus could benefit from vaccines. However, there are no data on vaccine responses in the MBL population. This article reviews the immunodeficiency of CLL and MBL, discusses the recommended vaccines and data on vaccine immunogenicity in patients with CLL, and outlines the need to develop more effective vaccine strategies in this population of patients at high risk for infection.

Introduction

Vaccination has been lauded as the most effective method to prevent infectious diseases. However, some populations do not reap the same protective benefits from vaccines as others. Predominant among these populations are patients with hematologic malignancies, who are particularly vulnerable to infections and in need of effective strategies to curb infection risk. Chronic lymphocytic leukemia (CLL) is one of the most common hematologic malignancies, comprising 11% of all hematologic malignancies, with an annual incidence in the United States approaching 15,000.[1] Infection is a major cause of mortality in patients with CLL, accounting for 30% to 50% of all deaths.[2] Strategies to reduce infections in patients with CLL have relied upon the administration of intravenous immunoglobulin (Ig), antimicrobial prophylaxis, treatment of the underlying disease, and vaccines. Despite the fact that certain vaccines are routinely recommended for patients with CLL (eg, influenza and pneumococcal vaccines), previous studies have shown low rates of immunogenicity in this population. Herein, we discuss the recommended vaccines for patients with CLL, comprehensively review the literature regarding the immunogenicity of these vaccines, provide an update on the currently known mechanisms of decreased vaccine immunogenicity, and propose solutions and the research needed to

provide more effective vaccine approaches for the CLL population. Furthermore, there are no data on the vaccine responses of individuals in the precursor state to CLL, which is monoclonal B-cell lymphocytosis (MBL). This population likely comprises 3% to 12% of adults past the age of 40 years.[3-7] Given the high prevalence of MBL, and the evidence that at least some individuals with MBL are at increased risk for infection,[8] we also discuss the need for research on vaccine efficacy in the MBL population.

Infection Risk in Monoclonal B-Cell Lymphocytosis and Chronic Lymphocytic Leukemia

Susceptibility to infection in CLL results from a complex immunodeficiency state that includes defects in innate, humoral, and cell-mediated immunity, which are present in most patients even before exposure to chemotherapy. MBL is characterized by the presence of clonal B cells in peripheral blood at a concentration below 5×10^9/L in the absence of lymphadenopathy, cytopenias, or autoimmune disease.[3,9,10] Although only a fraction of cases of MBL are clinically recognized (ie, patients with so-called high-count or clinical MBL), MBL is present in approximately 3% to 12% of the general population older than 40 years of age evaluated by sensitive testing.[3-7] A recent case-control study of community-based individuals with high-count MBL and CLL seen at Mayo Clinic demonstrated that individuals with clinical MBL are at a 3-fold higher risk of hospitalization for infection compared with a control population after adjustments for age, sex, and comorbidities.[8] Indeed, at 4 years after diagnosis, individuals with clinical MBL were approximately 4 times more likely to be hospitalized for infection than to require treatment for progressive CLL. The risk of hospitalization for infection among patients with MBL is similar to that among patients with CLL, both with a hazard ratio of approximately 3 relative to age-, sex-, and comorbidity-matched controls.[8] The extent and complete nature of the immunodeficiency in MBL have yet to be elucidated, but the immunodeficiency is thought likely to be due to the same mechanisms that cause immunodeficiency in CLL.

Only one study has characterized the most prevalent infections in the MBL population[8]; however, the literature regarding infectious complications in the CLL population is more extensive. The case-control study of infectious complications among patients with MBL or CLL revealed that infections with gram-positive organisms are more common among patients with CLL or MBL than in controls. *Staphylococcus aureus* was the primary pathogen identified from any culture site, with *Streptococcus pneumoniae* and *Pseudomonas* species next most common.[8] Other studies have demonstrated that *S pneumoniae* and *S aureus* are common pathogens in patients with CLL, and that the respiratory tract and bloodstream tend to be the most frequent sites of infection.[2,11,12] Although infections with these common bacterial agents often occur in patients who have untreated CLL, infections associated with immunosuppression (eg, invasive aspergillosis, nocardiosis, cytomegalovirus infection, *Pneumocystis jirovecii* infection) typically occur in patients who have received T-cell–depleting treatments for CLL (eg, purine analogues, alemtuzumab).[8,12] Recurrent viral infections, particularly those due to herpes simplex virus and varicella-zoster virus, are also more common after treatment,[13] whereas endemic mycoses tend to be associated with prolonged and profound neutropenia in patients with advanced disease.[14] To our knowledge, no studies have compared the rates and severity of respiratory infections caused by viral pathogens, such as influenza virus, among patients who have MBL or CLL with those in a control population.

Immunodeficiency That May Be Related to Impaired Vaccine Responses in Chronic Lymphocytic Leukemia

In the past, the immunodeficiency of CLL was thought to be due primarily to hypogammaglobulinemia, which affects approximately 25% of patients with CLL.[15] Patients with hypogammaglobulinemia tend to have an elevated risk for infections caused by bacteria, particularly encapsulated organisms.[11] There may be a particular infection risk related to Ig class deficiency; both IgG3 and IgG4 subclass deficiencies are associated with an increased risk of infection in patients with CLL.[16] IgG3 deficiency correlates with increased risk for herpes infection, and IgG4 deficiency correlates with respiratory tract infections.[17] IgA deficiency and defects in mucosal immune function may also be associated with an increased frequency of upper respiratory tract infections.[18] The pathogenesis of hypogammaglobulinemia is not completely elucidated but is at least related to a progressive decline in the numbers of functional B cells[13] and also to the suppression of residual normal B-cell function.[13,19] With fewer functional B cells, vaccines whose protection depends on adaptive humoral immunity will obviously be less effective in generating protective antibody responses for a given patient with CLL. Most current vaccines mediate protection mainly through the induction of highly specific serum IgG antibodies,[20] although a few live viral vaccines induce serum IgA and secretory IgA responses (ie, intranasal influenza virus and rotavirus vaccines, oral poliovirus vaccines).[20]

Although hypogammaglobulinemia clearly plays a role in infection risk,[16,21-23] newer studies have demonstrated that patients with CLL who have normal serum Ig

levels still remain at increased risk of infection.[8] In addition to decreased functional B-cell numbers and Ig levels, T-cell dysfunction occurs, even in the absence of chemotherapy.[24] Increases in T-regulatory cells,[25] decreases in T-helper activity, reversal of the CD4/CD8 ratio,[26] defects in natural killer cells,[27] increases in functionally naive T cells,[28] and impaired T-cell immunologic synapse[29] have all been reported. This T-cell dysfunction places patients at risk for infection with viral pathogens, as well as other pathogens, such as fungal and mycobacterial organisms. In terms of vaccination, T-cell dysfunction is of primary importance for vaccines that rely on T-cell–dependent B-cell responses. There is evidence that T-cell responses may contribute to the protection conferred by some live attenuated viral vaccines and possibly the acellular pertussis vaccine.[20] T-cell dysfunction likely plays a major role in the decreased responses to vaccines in CLL because patients with CLL have significant quantitative and qualitative abnormalities in T cells.

As noted, most current vaccines mediate protection through the induction of highly specific serum antibodies via B cells. There are 2 mechanisms by which an efficient and appropriate antibody response is accomplished. One mechanism is a T-independent response by which capsular polysaccharides elicit B-cell responses in the marginal zone and extrafollicular areas of the spleen and lymph nodes. Pure polysaccharide vaccines (Table 1) rely on a T-independent pathway to induce a humoral response. The other mechanism is a T-dependent pathway by which foreign peptide antigens are presented to the immune system and recruit antigen-specific CD4+ T-helper cells. Vaccines that rely on a T-dependent pathway to induce a humoral response include the following: glycoconjugate vaccines (in which a bacterial polysaccharide is conjugated to a protein carrier), toxoid vaccines, protein vaccines, and inactivated, live, or inactivated live viral vaccines (see Table 1).[20] For these vaccines, the combination of both B-cell dysfunction and T-cell dysfunction will affect vaccine responses.

Other mechanisms of immunodeficiency in CLL include neutropenia (as a side effect of chemotherapy or due to autoimmune granulocytopenia), abnormal complement activity, age, effects of chemotherapy, and effects of the corticosteroids used to treat CLL or associated autoimmune cytopenias. Immunosenescence related to age and impaired vaccine responses in older adults are multifactorial processes and topics of intense research.[30-32] Cytotoxic chemotherapy has multiple and various adverse effects on immune responses to vaccines.[33,34] In addition, corticosteroids, which are often given to patients with CLL in relation to treatment approaches or autoimmune complications, can dampen vaccine responses.[35-37] In general, the Advisory Committee on Immunization Practices (ACIP) immunization guidelines[38,39] and the Infectious Diseases Society of America (IDSA) immunization guidelines for immunocompromised patients[40] consider prednisone at a daily dose of 20 mg or higher (or its equivalent for other corticosteroids) for 2 weeks or longer as "high-dose" corticosteroid use, and immunosuppressive.

Vaccine Recommendations and Immunogenicity Studies in Chronic Lymphocytic Leukemia

MBL is considered a precursor state rather than a hematologic malignancy and is thus not currently classified as an immunocompromised state in the ACIP[38,39] or IDSA immunization guidelines.[40] Nonetheless, more recent data suggest that at least the subset of patients with clinical MBL are at high risk for infection and are probably best approached in a manner similar to that used for individuals with CLL. Patients with CLL are considered immunocompromised in the ACIP and IDSA immunization guidelines.

Influenza Vaccines

Annual influenza immunization is recommended for all persons in the United States aged 6 months or older. Accordingly, all patients with MBL or CLL should receive influenza vaccine annually. In the United States and many other parts of the world, high-dose influenza vaccines, with 4 times the amount of hemagglutinin compared with standard-dose influenza vaccines, have been licensed for adults 65 years of age or older. The ACIP and IDSA guidelines do not specifically endorse high-dose influenza vaccines over standard-dose influenza vaccines for adults aged 65 years or older who are immunocompetent or immunocompromised.[38,40] However, several studies have demonstrated increased immunogenicity for the high-dose influenza vaccine in immunocompetent adults aged 65 years or older.[41,42] Results of a large-scale, 2-season confirmatory efficacy trial involving more than 30,000 participants 65 years of age or older are expected to be released in 2014 by Sanofi Pasteur. Preliminary reports have indicated that Fluzone High-Dose (Sanofi Pasteur) has clinical efficacy superior to that of the standard dose of Fluzone (Sanofi Pasteur) in preventing influenza.[43]

In the United States, only aluminum adjuvant vaccines are approved by the US Food and Drug Administration (FDA). However, in Europe and many other parts of the world, oil-in-water adjuvants, such as AS03 (Adjuvant System 03, GlaxoSmithKline) and MF59 (Novartis), have been approved for influenza vaccination. Studies have shown increased immunogenicity, and in some cases increased efficacy, with these adjuvant vaccines in comparison with standard influenza vaccines in elderly persons aged 65 years or older[44-50] and in patients with hematologic malignancies.[51,52] In the future, updated guidelines

Table 1. Recommended and Contraindicated Vaccines for Patients With Chronic Lymphocytic Leukemia

Vaccine	Vaccine Type							
	Protein	Polysaccharide	Polysaccharide/Protein Conjugate	Toxoid	Killed Viral	Killed Bacterial	Live Attenuated Viral	Live Attenuated Bacterial
Advised to give in chronic lymphocytic leukemia								
Influenza	✔							
Pneumococcal polysaccharide		✔						
Pneumococcal conjugate			✔					
Tetanus toxoid (Td)				✔				
Pertussis, acellular (Tdap)	✔							
Diphtheria toxoid (Td or Tdap)				✔				
Permissible to give in chronic lymphocytic leukemia*								
Pertussis, whole cell						✔		
Hepatitis A					✔			
Hepatitis B	✔							
Hib polysaccharide		✔						
Hib conjugate			✔					
Japanese encephalitis (inactivated)					✔			
Meningococcal polysaccharide		✔						
Meningococcal conjugate			✔					
Polio, Salk					✔			
Rabies					✔			
Typhoid polysaccharide (injectable)		✔						
Contraindicated in chronic lymphocytic leukemia								
Influenza, intranasal							✔	
Measles							✔	
Mumps							✔	
Polio, Sabin							✔	
Rubella							✔	
Tuberculosis (BCG)								✔
Oral typhoid								✔
Varicella (chickenpox)							✔	
Varicella (zoster)							✔	
Yellow fever							✔	

Td, combined tetanus and diphtheria vaccine; Tdap, combined tetanus, diphtheria, and acellular pertussis vaccine; Hib, *Haemophilus influenzae* type b; BCG, bacille Calmette-Guérin.

* Indication for these vaccines depends on the patient's previous vaccination history, occupation, travel, and medical comorbidities.[38,39]

may recommend the use of high-dose influenza vaccines for adults aged 65 years or older. Once additional well-planned clinical trial studies have evaluated the safety and immunogenicity of the high-dose influenza vaccines in immunocompromised populations, we anticipate updated recommendations for these groups.

There are limited data regarding influenza vaccine immunogenicity in patients with CLL (Table 2). An older study, by Marotta and colleagues, evaluated the response to 2 doses of an inactivated whole-virus vaccine administered 31 days apart.[53] This study noted an association between vaccine response (defined as a hemagglutinin inhibition assay [HI] titer >1:10) and the absolute numbers of CD4+/CD45RA+ naive T cells and CD5– B cells.[53] It is difficult to extrapolate vaccine immunogenicity data from this study because the authors did not use a standard immunogenicity definition of seroconversion (a prevaccination HI titer <1:10 and a postvaccination HI titer ≥1:40, or a prevaccination HI titer ≥1:10 and a minimum 4-fold rise in postvaccination HI antibody titer) or of seroprotection (HI titer ≥1:40).[54] Another older study, by Bucalossi and colleagues, used the same definition of vaccine response as did the study of Marotta and colleagues. The investigators administered 2 doses of an inactivated influenza vaccine 31 days apart and noted an association between vaccine response and disease stage and between vaccine response and serum Ig levels.[55] It is difficult to draw meaningful inferences from these studies because they did not employ standard definitions of vaccine response.

The only study that defines influenza vaccine response by seroconversion (eg, 4-fold rise in postvaccination HI antibody titer to indicate seroconversion) is the 2001 study by van der Velden and colleagues. In this study, 20 patients with CLL at various Rai stages received 2 doses of an inactivated subunit vaccine 21 days apart. Seroconversion after 1 dose of vaccine was only 5% for influenza A strains H1N1 and H3N1 and was 15% for the influenza B strain in the vaccine. Seroconversion after 2 doses of vaccine was 15% for the 2 influenza A strains and 30% for the influenza B strain; however, vaccine response rates did not increase significantly after the booster dose.[56] Higher serum Ig levels correlated with protective HI titers for influenza B strains. Despite its small sample size, this is the only study in the literature providing information on the immunogenicity of the current influenza inactivated subunit vaccines. The results suggest that influenza vaccine seroconversion after a single dose in patients with CLL is approximately 5% for influenza A strains and 15% for influenza B strains. These responses are, of course, unacceptably low for a CLL patient cohort. Influenza vaccine serum antibody responses depend on age, preexisting antibody levels, and underlying medical conditions. A quantitative review of 31 influenza vaccine antibody response studies for standard-dose influenza vaccine found influenza seroconversion rates of roughly 60% for influenza A and B strains and seroprotection rates of roughly 80% for adults younger than 58 years. For those 58 years of age or older, the influenza seroconversion rates were 35% to 51% for influenza A and B, and the seroprotection rates were roughly 70%.[57] There are no data on responses to high-dose influenza vaccines in the CLL population, and this is clearly an attractive area for future study, given the data for improved responses noted in healthy adult controls.

Pneumococcal Vaccines

A conjugated 13-valent pneumococcal vaccine called PCV13 (Prevnar 13; Wyeth/Pfizer) was FDA approved in 2010 for use in children and licensed for adults in 2011. Starting in 2012, ACIP pneumococcal vaccine guidelines recommended use of PCV13 along with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) for immunocompromised adults aged 19 years and older, including those with congenital or acquired immunodeficiency, HIV infection, chronic kidney disease, nephrotic syndrome, leukemia, lymphoma, multiple myeloma, or other malignancy, and recipients of solid organ transplants.[58] Limited data on the immunogenicity of PCV13 in immunocompromised adults are available.[58,59] Similar or greater antibody responses to PCV13 compared with PPSV23 were found in immunocompetent adults.[60] According to ACIP guidelines, patients with CLL aged 19 years or older who have not previously received any pneumococcal vaccine should receive a dose of PCV13, followed by a dose of PPSV23 at least 8 weeks later (Table 3).[58] For patients who have previously received 1 or more doses of PPSV23, 1 dose of PCV13 should be given at least 1 year after the last PPSV23 dose. According to ACIP, a second PPSV23 dose is recommended 5 years after the first PPSV23 dose for patients with CLL who are younger than 65 years.[58] For those who require additional doses of PPSV23, the first dose should be given at least 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23 (see Table 3).[58] No further doses of PPSV23 are needed for patients vaccinated with PPSV23 at or after age 65 years.[58]

The schedule of pneumococcal vaccines (ie, order of conjugate and polysaccharide vaccines and interval between doses) has been shown to affect vaccine immunogenicity.[60,61] Patients who receive PPSV23 followed 1 year later by PCV13 have decreased antibody responses compared with those who receive PCV13 followed 1 year later by PPSV23.[62] These findings indicate that PCV13 augments the immune response to a subsequent dose of PPSV23 administered 1 year later for serotypes in common. Various study schedules of PCV13 and PPSV23 have confirmed that PCV13 is the preferred first choice for immunization of naive healthy adults to optimize antibody response, induction of memory, and maintenance of long-term protection. There have been concerns that repeated vaccination with pneumococcal polysaccharide vaccines may cause immune tolerance or vaccine hyporesponsiveness.[63]

Table 2. Immunogenicity Studies of Influenza Vaccine in Patients With Chronic Lymphocytic Leukemia

First Author	Study Type	Vaccine, Manufacturer; Dosing	Patient Data	Percentage With Hypogammaglobulinemia (<6.2 g/L)	Percentage With Chemotherapy/ Steroids	Immunogenicity Endpoint and Correlates
Van der Velden,[56] 2001	Prospective cohort HI at days 0, 21, 42	Influvac (inactivated subunit) Duphar, Amsterdam, the Netherlands 2 doses, 21 days apart	n=20 Rai 0, 20% Rai I/II, 40% Rai III/IV, 40%	15%	7 of 20 with previous chemotherapy, none in past 3 months	Seroconversion after 1 dose: 5% for H1N1 and H3N1, 15% for B. Seroconversion after 2 doses: 15% for H1N1 and H3N2, 30% for B. No significant increase in conversion or protection rates after booster. Influenza B: higher immunoglobulin levels were correlated with seroconversion.
Marotta,[53] 1998	Prospective case-control HI at days 0, 30, 60	Isiflu Zonale (inactivated virus vaccine) Istituto Sierovaccinogeno, Naples, Italy 2 doses, 31 days apart	n=18, CLL Binet A, 50% Binet B, 22% Binet C, 28% n=15, sex- and age-matched controls	22%	Not reported, no chemotherapy in past 4 weeks	Did not assess seroconversion. Defined response as seroprotection with HI titer >1:10. Correlation between response and absolute numbers of both CD4+/CD45RA+ naive T cells and CD5– B cells was found.
Bucalossi,[55] 1995	Prospective case-control HI at days 0, 30, 60	Inflexal Berna (inactivated whole virus) Istituto Sieroterapico Berna, Como, Italy 2 doses, 31 days apart	n=30, CLL Binet A, 30% Binet B, 40% Binet C, 30% n=30, sex- and age-matched controls	Not reported	Not reported	Did not assess seroconversion. Defined response as seroprotection with HI titer >1:10. Correlation between response and disease stage. Correlation between responses and immunoglobulin levels.

HI, hemagglutinin inhibition assay.

Not all countries recommend repeated doses of PPSV23 for immunocompromised adults. Studies have shown that vaccine hyporesponsiveness does not seem to occur with repeated PPSV23 vaccination if more than 5 years have elapsed since the previous PPSV23 dose.[64-66] Thus, ACIP recommends a period of 5 years or more between repeated PPSV23 doses (see Table 3).[38,39]

Two studies have evaluated responses to pneumococcal vaccines in patients with CLL. One studied responses to the 23-valent polysaccharide pneumococcal vaccine, and the other studied responses to the 7-valent pneumococcal conjugate vaccine (Table 4). In the study of the polysaccharide vaccine, none of the 25 subjects had previously received the pneumococcal vaccine. The rate of response, defined as a 2-fold or greater increase in postvaccination serotype-specific IgG over prevaccination levels for at least 2 of 3 serotypes tested, was 22%. An adequate response to vaccination was seen only in patients with serum IgG levels in the normal range.[67] In the study of the 7-valent conjugate pneumococcal vaccine, none of the subjects had previously received either the polysaccharide or conjugate pneumococcal vaccines. In patients with CLL, the rate of vaccine response, defined as a 2-fold or greater increase in serotype-specific IgG and a postvaccination level of 0.35 µg/dL or higher for 6 of the 7 serotypes, was 24%, and the rate of vaccine response was 71% in controls (P<.001).[68] The authors of this study noted that when the analysis was restricted to patients with Binet A disease, no prior chemotherapy, and no hypogammaglobulinemia, then 39% (11 of 28) of the patients with CLL responded to 6 serotypes, compared with only 5% (1 of 21) of the patients with CLL not meeting these 3 criteria (P<.007).[68] This

Table 3. Recommendations for Vaccines Indicated in All Patients With Chronic Lymphocytic Leukemia [a]

Influenza vaccines			
Age <65 y	Annual standard dose of inactivated influenza vaccine		
Age ≥65 y	Annual standard dose or high dose of inactivated influenza vaccine		
Tetanus-diphtheria, pertussis (Td, Tdap) vaccines			
No previous Tdap after age 11 y	Tdap regardless of interval since most recent Td vaccine and Td booster every 10 y thereafter		
Previous Tdap dose after age 11 y	Td booster every 10 y		
Pneumococcal vaccines			
PPSV23 vaccine history (number of previous doses)			
0	PCV13 first, followed by PPSV23	Second PPSV23 [b]	PPSV23 at 65 y [b] Adults who receive a dose of PPSV23 at age ≥65 y do not need another dose.
1	PCV13	Second PPSV23 [b]	
2	PCV13		

Td, combined tetanus and diphtheria vaccine; Tdap, combined tetanus, diphtheria, and acellular pertussis vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, conjugated 13-valent pneumococcal vaccine; w, weeks; y, years.

[a] Indication for other vaccines depends on the patient's previous vaccination history, occupation, travel, and medical comorbidities.[38,39]

[b] Additional doses of PPSV23 should be administered 5 years or more after the previous PPSV23 dose if the patient is younger than 65 years of age.

would suggest that patients should be vaccinated early in the course of their disease and before the onset of hypogammaglobulinemia. However, the 39% response rate is still suboptimal for this patient group. Whether the new approach of PCV13 followed 8 weeks later by PPSV23 will improve immunogenicity in the CLL population merits evaluation.

Tetanus, Diphtheria, and Acellular Pertussis Vaccines

The tetanus-diphtheria (Td) vaccine should be administered every 10 years. According to Centers for Disease Control and Prevention ACIP recommendations, a single dose of acellular pertussis vaccine is recommended for previously unvaccinated persons aged 11 years or older.[38,39] Therefore, all patients with CLL should receive a dose of tetanus-diphtheria-acellular pertussis (Tdap) vaccine if they have not yet received one in adulthood. Given the age of most patients with CLL, they would not have received the Tdap vaccine as adolescents because this vaccine is relatively new. The Tdap vaccine should be given even when the last Td vaccine was administered less than 10 years ago.[38,39] Data on tetanus vaccine responses in CLL are sparse, and there are no data on responses to pertussis vaccines in CLL. One study noted decreased antibody responses to tetanus toxoid vaccine in patients with CLL compared with a control population. Higher rates of antibody responses to tetanus toxoid antigen were noted in those with early-stage disease and in those with normal serum Ig levels, a finding that would argue in favor updating Td vaccination shortly after diagnosis.[69]

Data regarding other vaccine responses in patients with CLL are scarce.[70] Responses to the tetanus toxoid–*Haemophilus influenzae* type b conjugate vaccine have ranged from 21% to 48% of patients with CLL.[67,69,71]

Vaccines to Avoid

In general, individuals with CLL should not receive any live attenuated viral or live attenuated bacterial vaccines (see Table 1). The contraindicated vaccines include intranasal influenza, measles, mumps, rubella, Sabin polio, bacille Calmette-Guérin (BCG), oral typhoid, varicella (chickenpox and zoster), and yellow fever vaccines. This recommendation is based upon the ACIP[38,39] and IDSA[40] recommendations for immunocompromised persons. In a person with an inadequate immune system, there is the potential for a live vaccine to cause infection.

Strategies to Increase Vaccine Immunogenicity in Patients With Chronic Lymphocytic Leukemia

Based on the fact that plasma histamine levels have been observed to be higher in patients with CLL than in healthy controls,[71] some have suggested that the production of antibodies against vaccines might be enhanced by blocking histamine type 2 receptors with ranitidine. Indeed, 2 small trials have suggested that ranitidine improves T-cell–dependent antibody responses to the *H influenzae* conjugate vaccine.[71,72] However, ranitidine has not been successful in improving influenza vaccine[71] or polysaccharide pneumococcal vaccine[72] antibody responses. Although others have hypothesized that granulocyte-monocyte colony-stimulating factor (GM-CSF) might improve vaccine responses in patients with CLL, GM-CSF did not

Table 4. Immunogenicity Studies of Pneumococcal Vaccine in Patients With Chronic Lymphocytic Leukemia

First Author	Study Type	Vaccine, Manufacturer; Dosing	Patient Data	Percentage With Hypogammaglobulinemia (<6.2 g/L)	Percentage With Chemotherapy/ Steroids	Immunogenicity Endpoint and Correlates
Hartkamp,[67] 2001	Prospective Specific IgG titers against serotypes 3, 4, and 9 at days 0 and 21	Pneumovax 23; Merck Sharp & Dohme 1 dose	n=25, B-CLL Rai 0, 40% Rai I/II, 44% Rai III/IV, 16% Mean age, 70	Not reported	32% with previous chemotherapy, none with chemotherapy 3 months before study	Response rate defined as ≥2-fold serotype-specific IgG increase for at least 2 of 3 serotypes tested; 22% responded. Response seen only in those with normal total IgG levels. Soluble CD23 levels were significantly lower in those with response.
Sinisalo,[68] 2007	Prospective case-control Specific IgG titers against all 7 serotypes at days 0 and 21	Prevnar Pneumococcal 7-valent Conjugate Vaccine; Wyeth/ Pfizer 1 dose	n=49, CLL Binet A, 80% Binet B, 18% Binet C, 2% n=24, age- and sex-matched controls Mean age, 65	29%	22% with present or past chemotherapy, 16% with ongoing steroids	Response rate defined as ≥2-fold serotype-specific IgG increase + postvaccination level of ≥0.35 µg/dL. Response to at least 6 serotypes: 24% in CLL patients and 71% in controls (P<.001). Statistically significant increase in response rate for controls vs CLL patients for all serotypes. If Binet A, before chemotherapy, and no hypogammaglobulinemia, then 39% (11 of 28) of CLL patients responded to 6 serotypes, compared with only 5% (1 of 21) of other patients (P<.007).

IgG, immunoglobulin G; CLL, chronic lymphocytic leukemia.

improve polysaccharide pneumococcal vaccine antibody responses in controlled trials.[73] Lenalidomide has been shown to improve conjugate pneumococcal vaccine responses in patients with multiple myeloma.[74] Increases in serum Ig levels have been observed in patients treated with lenalidomide (Revlimid, Celgene).[75] Lenalidomide merits further testing as a vaccine adjuvant in patients with CLL.

New Directions

Strategies to increase vaccine immunogenicity in patients with CLL will likely not be a "one size fits all" approach. One plausible hypothesis is that some adjuvants will work for T-cell–dependent antibody responses and others will work for T-cell–independent antibody responses. In order to come up with rationally designed adjuvant strategies, we need to have a far better understanding of the mechanisms that lead to impaired vaccine responses in these patients. We propose that through detailed vaccinomics studies of vaccine responses in patients with CLL and in healthy age-matched controls, designed to uncover the exact mechanism(s) involved in deficient vaccine responses, we will be able to better elucidate the strategies that can be used to overcome these factors. *Vaccinomics* is the comprehensive study of immune responses to vaccines such that these responses can be understood, predicted, and then applied to the rational and directed development of vaccines.[76-78] It relies upon the integration of the tools of transcriptomics, proteomics, epigenomics, immunogenetics, computational modeling, and immune monitoring.[76,79] To a certain extent, our own studies on leukemic cell–stromal cell interactions have set the stage for such vaccinomics studies. In brief summary, there is significant evidence that leukemic B cells are profoundly immunosuppressive and modify stromal cell function to

favor disease progression.[74-79] Vaccines have historically been developed based on an approach that included isolating a pathogen, inactivating or attenuating it, and then injecting it into a host. However, with a reliance upon the "-omics" tools listed above, which have allowed insights into individualized medicine, more informed vaccines and adjuvants can be designed to target subgroups of interest, such as immunosenescent populations, groups with common genetic variants that may impede the development of protective immune responses, and patients with malignant diseases, such as CLL, that cause profound immunosuppression.[76,80-85]

The first steps in improving vaccine responses in CLL should include the detailed study of already-approved vaccines and schedules that have not yet been evaluated in this patient population: high-dose influenza vaccine, oil-in-water adjuvant influenza vaccines currently licensed in Europe, and various combinations of the polysaccharide and conjugate pneumococcal vaccines that patients will be receiving as a result of the new pneumococcal vaccine guidelines. These studies should be designed so as to provide a clear understanding of the depth of vaccine responses in all stages of CLL and in the clinical MBL cohorts, including innate immune, adaptive humoral, cytokine, and cell-mediated immune responses.

With regard to MBL, no one has reported vaccine responses in MBL populations. As noted before, up to 3% to 12% of the healthy population may be found to have MBL. If individuals with these small, highly prevalent B-cell clones show suboptimal responses to vaccines, they may represent an important public health issue pertaining to deficient vaccine responses. If indeed individuals with MBL are not able to mount appropriate responses to vaccines, then alternative vaccine strategies, such as are administered to other immunocompromised groups, may need to be considered for use in this population.

Summary

Individuals with CLL appear to be at increased risk for infection, and evidence suggests that they have an inadequate response to most routinely used vaccines. Clinical trials are needed to address a number of key questions related to vaccine use in patients with CLL: (1) What are the seroconversion or seroprotection levels for all disease stages of CLL in response to specific vaccines? (2) What are the mechanisms of dysfunction related to suboptimal responses in CLL? (3) Do alternative vaccine preparations overcome the poor responses to certain pathogens? (4) Can vaccine adjuncts enhance responses to existing vaccines? (5) Can vaccinomics studies be employed in this patient population to elucidate and overcome the mechanisms responsible for decreased vaccine responses? Determining the responses to vaccines in patients with both low-count and high-count MBL will also be critically important and may have public health implications, given the prevalence of this condition. It is hoped that newer vaccines, alternative vaccination schedules, and the use of vaccine adjuvants may increase responses to vaccines in patients with CLL and reduce the number of deaths due to infection in this population of immunosuppressed patients.

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