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BRIEF COMMUNICATION

Effect of Ibrutinib on Hmphocytic Leukemia: a Single-Center Experience

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Abstract

Objective/Background: **In the era of novel agents, Bruton tyrosine kinase (BTK) inhibitors have changed the dynamics of treating chronic lymphocytic leukemia. However, small studies have shown conflicting results regarding the additive humoral dysfunction with their use.**

Methods: **We prospectively compared vaccine responses in patients on ibrutinib ($n = 10$) with matched controls ($n = 16$) and analyzed whether a protein-based (tetanus-diphtheria toxoid) or a carbohydrate (Pneumovax) moiety will result in an improved immunological response.**

Results: **An appropriate serological response in IgG titers for diphtheria was seen in 40% of patients on ibrutinib and 31% of patients in the control group. About 30% of patients on ibrutinib and 44% of patients in the control group had an adequate response to tetanus toxoid. None of the patients on ibrutinib mounted an adequate response to Pneumovax, while 31% of patients in the control arm responded appropriately. These differences in the results were considered insignificant as all p values were greater than the cut-off of 0.05.**

Conclusion: **Our study did not show significant detrimental vaccine responses with ibrutinib and calls for larger multicenter studies to elucidate long-term effects, especially in patients with prior exposure to anti-CD20 monoclonal antibodies.**

Keywords: Antibody, B-cell, Chronic, Humoral, Immune response, Immunization, Immunoglobulin, Leukemia, Lymphocytic, Pneumococcal, Tetanus-diphtheria

Despite significant advancements in the management of chronic lymphocytic leukemia (CLL) over the past two decades, infections remain the most common cause of death and account for up to 80% of disease-related mortality [1]. Multiple factors contribute to increased susceptibility to infection in patients with CLL, including both disease-related humoral and cell-mediated immune defects, along with iatrogenic immunosuppression and marrow toxicity caused by chemo-immunotherapy regimens [2].

Ibrutinib is an irreversible inhibitor of Bruton tyrosine kinase (BTK) affecting B-cell proliferation and survival. Ibrutinib is currently recommended as the first-line treatment of naive del17/TP53 mutated and all refractory/relapsing CLL patients by the National Comprehensive Cancer Network 2020−21 and European Society for Medical Oncology guidelines [3−5]. Although multicenter randomized clinical trials have shown ibrutinib to be well tolerated with less adverse effects compared with conventional chemotherapy, downstream effects of BTK

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inhibitors (BTKi) lead to IgG hypogammaglobulinemia and potentially increased risk of infection [2,3,6]. Infection prophylaxis with vaccinations is the standard of care for CLL patients, particularly vaccination against *Streptococcus pneumoniae,* which is a common pathogen for sinopulmonary disease that leads to significant morbidity and mortality [7]. Data regarding vaccine responses in patients with CLL are scarce, with a few small studies suggesting suboptimal responses to influenza and both polysaccharide (PPV23) and conjugated (PCV13) forms of pneumococcal vaccinations [8–11]. Our study aims to add clarity regarding the effects of ibrutinib on humoral immune responses to both polysaccharide and peptide antigens.

This prospective, non-blinded, single-center study compared the efficacy of immunization with peptide antigens (diphtheria and tetanus toxoid; Td vaccine) and a polysaccharide antigen (*S. pneumoniae;* PPV23 vaccine) in CLL patients currently on treatment with ibrutinib (treatment group, $n = 10$) as compared with CLL patients on wait-and-watch approach and/or distant treatment regimens other than BTKi (control group, $n = 16$). We enrolled patients with flow cytometry–confirmed CLL and/or small lymphocytic lymphoma, age $\geq$ 40 years, and their matched controls with an Eastern Cooperative Oncology Group performance status < 2 after informed consent. The study excluded patients with previously diagnosed primary immunodeficiency, ongoing immunoglobulin replacement, and those treated with monoclonal anti-CD20 antibodies (rituximab or obinutuzumab) in the past 6 months or those who received vaccination with Td or PPV23 within the last 10 and 5 years, respectively.

We collected patient demographics, baseline serum IgG, and specific IgG titers for tetanus, diphtheria, and 23 serotypes for *S. pneumoniae*. Patients in both groups then received vaccination with Td and PPV23, with repeat disease-specific IgG titers (Table 1) assessed at 4 ± 1 week. An adequate response to tetanus and diphtheria was defined as a two-fold increase in specific IgG in the protective range (0.1 IU/mL). An adequate response to PPV23 was defined as > 70% of the 23 pneumococcal serotypes demonstrating a two-fold increase from baseline if pre-vaccination specific IgG were ≥1.3 mcg/mL, or a four-fold increase from baseline if pre-vaccination specific IgG were <1.3 mcg/mL [12]. The primary outcome was an adequate response to vaccination with Td and PPV 23 compared between the treatment and control groups. Fischer's exact test was performed to evaluate the odds ratio (OR) of response to each vaccination while on treatment with ibrutinib.

The median age was 65 (interquartile range [IQR]: 60–68) years in the treatment group and 69 (IQR: 65.5–75) years in the control group. Patients were on ibrutinib for a median time of 1.3 (IQR: 0.4–2.8) years in the treatment group. The median baseline IgG levels were similar in the treatment group (650 mg/dL) and control group (733 mg/dL). An adequate response in IgG for diphtheria was seen in 40% (4/10) of patients in the treatment group, and 31.3% (5/16) in the control group (OR: 1.44; 95% confidence interval [CI]: 0.20–10.07; $p = .69$).

Table 1. Baseline Characteristics and Vaccination Responses.

Characteristics	Ibrutinib group, $n = 10$	Control group, $n = 16$
Sex		
Male	7 (70)	13 (81)
Female	3 (10)	03 (19)
Age (yr)	69 (65.5–75)	69 (65.5–75)
Time since diagnosis (yr)	4.65 (1.7–9.1)	5.55 (2.6–17.1)
Time since on ibrutinib (yr)	1.3 (0.4–2.8)	–
Number of ABx courses[a]	2 (2–3)	0 (0–1)
Pre-vaccination IgG, mg/dL	650 (544–820)	733 (468.5–827)
Previous exposure to rituximab[b]	4 (40)	2 (12.5)
Vaccination responses[c], responders		
Streptococcus pneumoniae	0 (0)	5 (31.3)
Diphtheria	4 (40)	5 (31.3)
Tetanus	3 (30)	7 (43.8)

Note. Data are presented as *n* (%) or median (IQR). ABx = antibiotics; IQR = interquartile range (IQR_1–IQR_3); *n* = total number of patients.

[a] In the year prior to enrollment.

[b] Majority of the exposure was >1 year prior to initiation of ibrutinib.

[c] Response to vaccination is defined as a two-fold increase in specific IgG into the protective range, that is, >1.3 IU/mL for tetanus and diphtheria. For Prevnar 13, an adequate response was defined as a two-fold increase from baseline if pre-vaccination specific IgG were ≥1.3 mcg/mL, or if titers increased by four-fold from baseline if pre-vaccination specific IgG were <1.3 mcg/mL, for >70% of the serotypes.

Furthermore, 30% (3/10) of patients in the treatment group and nearly half (7/16) of the patients in the control group demonstrated an adequate response to tetanus toxoid (OR: 0.34; 95% CI: 0.03–2.53; p = .40). Response to PPV23 was notably absent in patients of the treatment group as none of them demonstrated seroconversion, while 31% (5/16) of patients responded in the control group; however, the overall results were not significant (OR: 0.00; 95% CI: 0.00–1.57; p = .12; Fig. 1; Table 1). Additionally, the results of a logistic regression model showed age, sex, and baseline IgG levels to have no correlation with the response to any of the vaccines (all p values > 0.05). Furthermore, a secondary logistic regression model also revealed that treatment with ibrutinib did not alter response for any of the vaccines (p = .99 for diphtheria, p = .99 for tetanus, and p = .49 for PPV23).

Our data suggest that treatment with ibrutinib does not have a significant effect on vaccination responses to polysaccharide or peptide antigens. All patients with CLL, regardless of being on observation therapy or treatment with ibrutinib, demonstrated suboptimal humoral function as evidenced by poor response to vaccinations despite adequate serum IgG. In current practice, hematologists generally stratify for infectious complications by checking total serum IgG, and often consider immunoglobulin replacement therapy in patients with low serum IgG, typically < 400 mg/dL [7]. Our data suggest that checking vaccine responses is a better indicator of humoral dysfunction than serum IgG alone.

Previous studies have shown mixed results with polysaccharide (pneumococcal), peptide (influenza) antigens, and recombinant adjuvant inactivated viral particles (hepatitis B surface antigen and glycoprotein E from varicella zoster), particularly in advanced CLL [8,10,11,13]. Sun et al. [14] demonstrated a decline in the rate of infections in CLL patients if they experienced an increase in serum IgA ≥ 50% at 12 months, thought to be secondary to cross talk between BTK and B-cell activating factor (BAFF) signaling pathways. However, despite the decreased number of infections, the group also showed that only about 26% of patients achieved statistically significant seroprotective titers for at least one strain with influenza vaccination [15]. High rates of seroconversion (75%) were seen in response to the recombinant varicella zoster glycoprotein E (rVZgE) vaccine by Zent et al. [16]. On the contrary, Andrick et al. [17] found an increased expression of SAMSN1 gene in B cells secondary to BTK inhibition that ultimately leads to decreased production of IgM, resulting in a suboptimal response to PCV13. Douglas et al. [18] also cited ibrutinib-related

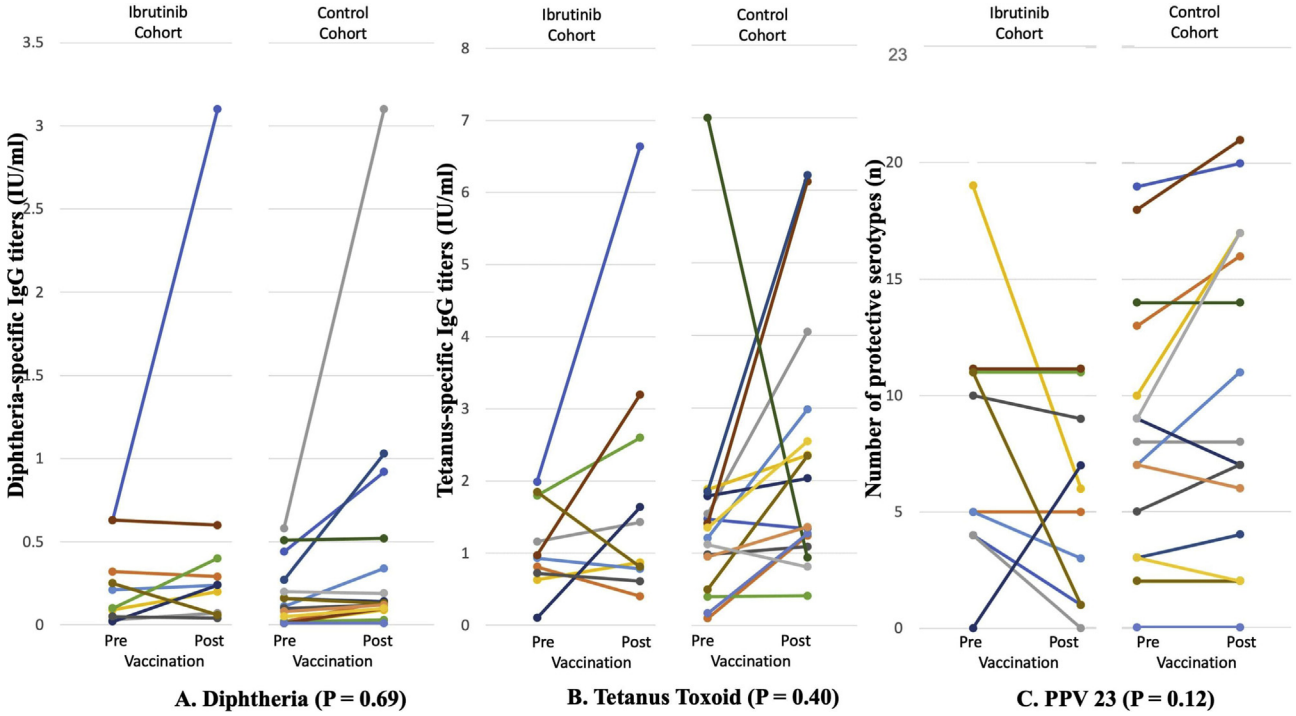

Fig. 1. Individual patient pre- and post-vaccination specific IgG titers for (A) diphtheria and (B) tetanus toxoid and (C) the pre- and post-vaccination number of protective serotype antigens for pneumococcal polysaccharide vaccine, PPV23. Treatment group (n = 10); control group (n = 16).

immune dysfunction as the reason for lower response to influenza vaccine (7%) seen in their cohort. A 2020 study by Pleyer et al. [19] concluded that BTKi particularly decreased de novo immune response to hepatitis B vaccine compared with recall immune response to rVZgE vaccine because of stunned antigen-specific Ig production. Therefore, these studies that have evaluated the potential contribution of ibrutinib to humoral dysfunction have revealed mixed results. Decreased vaccination response is seen especially with influenza, hepatitis B, and PCV13 vaccination, and improved primary immune response is seen with the recombinant rVZgE [15–19]. Our study suggests that humoral dysfunction in patients with CLL stems from inherent defects due to CLL rather than the effect of ibrutinib. This becomes even more relevant in the current discussion of the appropriateness and effectiveness of mRNA-based vaccines for SARS-CoV-2 in CLL patients who are actively taking BTKi [20].

The strength of our study is the prospective design with the median length of ibrutinib therapy being over a year. Our approach to immune evaluation in CLL with vaccine responses is also novel and well described in other disease states, such as primary immunodeficiency. However, we acknowledge important limitations, most notably a small sample size. Five patients were also previously treated with rituximab before initiation of ibrutinib, and although this was not within the past 6 months, anti-CD20 therapies can have long-lasting B-cell suppressive effects [21]. Our study assessed vaccine responses but did not evaluate B-cell memory, which may be suboptimal in CLL patients with or without ibrutinib. Our center has shown similar defects in long-lasting immunity in patients with multiple myeloma that initially responded to vaccination with PCV13, but the IgG response waned within 6 months [22]. Finally, our study did not formally track infectious complications, which may not directly correlate with our proposed laboratory evaluation.

In conclusion, our results demonstrate that patients with CLL have humoral dysfunction as evidenced by suboptimal response to vaccination, and this dysfunction is not worsened by therapy with ibrutinib. Larger studies on the effects of BTKi are needed to further elucidate their role on humoral immunity and infections in patients with CLL.

Authors' contributions

H.H. and M.A.U. are co-first authors and equally contributed to patient consent, data extraction, literature review, formulating tables, analyzing the data, and wrote the paper. S.J., J.B., and S.S.M. provided a supervisory role, critically appraised the manuscript, and provided oncological and immunological care to patients. J.B. also performed the statistical analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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