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Seasonal Influenza Vaccination in Patients With Chronic Lymphocytic Leukemia Treated With Ibrutinib

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Chronic lymphocytic leukemia (CLL) is associated with immune dysfunction. Infections account for up to 60% of deaths in patients with CLL.[1] To lessen infectious complications, immunization against influenza for immunocompromised individuals is recommended.[2] However, patients with CLL have impaired responses to vaccines, which are further reduced by hypogammaglobulinemia and chemotherapy.[3]

Ibrutinib, an irreversible inhibitor of Bruton tyrosine kinase, is approved for the treatment of CLL and other B-cell malignant neoplasms.[4] Bruton tyrosine kinase is essential for B-cell receptor signaling, B-cell maturation, and immunoglobulin synthesis. Inactivating mutations in *BTK* (OMIM 300300) cause X-linked agammaglobulinemia, an immunodeficiency characterized by severe hypogammaglobulinemia and recurrent infections. In patients receiving ibrutinib, it is unknown whether B cells can mount a humoral immune response to vaccination.

Methods |

Influenza vaccination was offered to patients enrolled in a phase 2 trial of single-agent ibrutinib (NCT01500733). Between October 1 and November 21, 2014, a total of 19 patients received 1 dose of inactivated trivalent influenza vaccine containing A/California/7/2009 (A/CA/09; H1N1) pdm09, A/Texas/50/2012 (A/TX/12; H3N2), and B/Massachusetts/2/2012 (B/MA/12) viruses. Patients 65 years or older received Fluzone high-dose vaccine (Sanofi Pasteur).[5] Patients younger than 65 years received Fluzone high-dose or standard-dose Afluria vaccine (bioCSL) depending on availability of the vaccines. Study procedures were approved by the National Heart, Lung, and Blood Institute institutional review board. All patients provided written informed consent.

We measured hemagglutinin inhibition antibody titers before and 3 months after vaccination. Standard criteria were used to define seroconversion (increase in hemagglutinin inhibition titer from <1:10 to ≥1:40 or a ≥4-fold increase in hemagglutinin inhibition titer ≥1:10 at baseline) and seroprotection (hemagglutinin inhibition titer ≥1:40). Infectious symptoms were recorded during the following 6 months. The Centers for Disease Control and Prevention case definition[6] for influenzalike illness was used.

With 19 patients, the study had 87% power to detect a 25% difference in response rate against the null hypothesis (response rate ≤5%) with 1-sided $P < .05$ considered significant using a binomial test. Geometric mean titers before and after vaccination and seroprotection rates were compared using the Wilcoxon signed rank test and McNemar test, respectively. Statistical analysis was performed by *R*, version 3.2.3 (R Foundation for Statistical Computing).

Results |

Seroconversion for at least 1 strain was observed in 5 patients (26%; 95% CI, 9.2%−51.2%) and the null hypothesis was rejected ($P = .002$). Seroconversion for the A/CA/09, A/TX/ 12, and B/MA/12 strains occurred in 3 (16%; 95% CI, 3.4%−39.6%), 5 (26%; 95% CI, 9.2% −51.2%), and 2 (11%; 95% CI, 1.3%−33.1%) patients, respectively.

There were significant increases in geometric mean titers against all 3 viruses (A/CA/09: before vaccination, 19.3 [95% CI, 10.4–35.7]; after vaccination, 27.8 [95% CI, 12.8–60.3]; *P* = .04; A/TX/12: before, 17.9 [95% CI, 9.4–34.1]; after, 38.6 [95% CI, 19.3–77.0]; *P* = .002; B/MA/12: before, 9 [95% CI, 5.7–14.0]; after, 12.9 [7.5–22.1]; *P* = .02) and in seroprotection rate against the A/TX/12 strain (32% vs 74%; *P* = .004) after vaccination (Table). Influenza vaccination during the 2013–2014 season was not associated with higher prevaccination or postvaccination titers in the 2014–2015 season.

Seven patients (37%) developed influenzalike illness within 6 months of vaccination. One patient had grade 3 infection with influenza A, subtype H3; all other patients had grade 1 to 2 influenzalike illness.

Discussion |

To our knowledge, this is the first study reporting immunization response in patients with CLL treated with ibrutinib. In a small cohort of patients, we sought to test the hypothesis that Bruton tyrosine kinase inhibitors abrogate humoral response to antigen. Given our data, additional studies are warranted to evaluate whether ibrutinib impairs or improves vaccine response relative to other treatments.

Limitations of the study include a small sample size and incomplete laboratory confirmation of influenza infection. Furthermore, defining an appropriate control group may prove challenging; treatment-naive patients often have immune impairment related to their disease while patients in remission after chemoimmunotherapy may experience the immunosuppressive effects of treatment.[7]

Conclusions |

Our data show that an antibody response to influenza vaccination is permissible in patients receiving single-agent ibrutinib. Up to 74% of patients achieved seroprotective titers against common influenza viruses after vaccination. Consequently, routine immunization against influenza should be considered in accordance with the Centers for Disease Control and Prevention recommendations for immuno-compromised patients.[2]

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Table.

Titers Before and After Influenza Vaccination

Titer	Before Vaccination	After Vaccination	*P* Value
GMT (95% CI)			
A/CA/09	19.3 (10.4–35.7)	27.8 (12.8–60.3)	.04
A/TX/12	17.9 (9.4–34.1)	38.6 (19.3–77.0)	.002
B/MA/12	9 (5.7–14.0)	12.9 (7.5–22.1)	.02
HAI Titer ≥1:40, No. (%) [95% CI][a]			
A/CA/09	8 (42) [20.3–66.5]	10 (53) [28.9–75.6]	.25
A/TX/12	6 (32) [12.6–56.6]	14 (74) [48.8–90.9]	.004
B/MA/12	2 (11) [1.3–33.1]	5 (26) [9.2–51.2]	.13

Abbreviations: A/CA/09, A/California/7/2009; A/TX/12, A/Texas/50/2012; B/MA/12, B/Massachusetts/2/2012; HAI, hemagglutination inhibition assay; GMT, geometric mean titer.

[a]The number corresponds to the number of patients with HAI titer ≥ 1:40 for each virus. The numbers do not total 19 since every patient is represented in each row.