Analysis of Efficacy and Tolerability of Bruton Tyrosine Kinase Inhibitor Ibrutinib in Various B-cell Malignancies in the General Community: A Single-center Experience

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Abstract

Ibrutinib, a novel Bruton tyrosine kinase inhibitor, has revolutionized the treatment of various B-cell malignancies. In this retrospective study, we analyzed the data of 45 patients with various B-cell malignancies to determine ibrutinib's clinical efficacy and adverse effects in a real-world setting. Results showed an excellent efficacy and a favorable toxicity but a higher incidence of atrial fibrillation.

Background: Ibrutinib, an irreversible inhibitor of Bruton tyrosine kinase (BTK), is a novel drug that has shown significant efficacy and survival benefit for treatment of various B-cell malignancies. The primary objective of the present study was to investigate the efficacy of ibrutinib therapy in various B-cell malignancies in the general community. The secondary objectives included studying the adverse effects, ibrutinib-induced peripheral lymphocytosis, and effect on immunoglobulin levels. **Patients and Methods:** The present study was a retrospective observational cohort analysis conducted at Abington Jefferson Health. The clinical response was determined from the hematologist's assessment and evaluated independently using the response criteria for each B-cell malignancy. Adverse effects were graded according to the Common Terminology Criteria for Adverse Events, version 4.0. The Wilcoxon signed-rank test was used to compare immunoglobulin levels before and after ibrutinib. Forty five patients with B-cell malignancies and receiving ibrutinib therapy were eligible. **Results:** The median age was 73 years (range, 49-96 years), and 84.4% of the patients had received $\geq$ 1 previous therapy. The best overall response rate of all cohorts combined was 63.8%. The greatest overall response rate was observed in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (76.1%), followed by those with Waldenström macroglobulinemia (75%). Of the 45 patients, 88.9% experienced adverse effects. Antiplatelet activity of ibrutinib was most commonly observed (30.5%). Of note, 5 patients (11%) developed new-onset atrial fibrillation after drug initiation. Peripheral lymphocytosis after drug initiation was observed in most patients, with a peak level at 1 month (median lymphocyte count, 2.7×10^3 cells/μL). Although the IgG levels at 3, 6, and 12 months had decreased ($P = .01$ for all) compared with the levels before ibrutinib, the IgA levels had not increased at 3, 6, 12, and 24 months ($P = .6$, $P = .5$, $P = .3$, and $P = .9$, respectively). **Conclusion:** Ibrutinib is a highly effective and tolerable drug for B-cell malignancies in the general community. In contrast to the previously reported rate of 5% to 7%, we observed a higher rate (11%) of atrial fibrillation, which might have resulted from the smaller sample size in the present study and the multiple comorbidities. Nonetheless, this treatment-limiting side effect requires further elucidation. Paradoxical lymphocytosis at the outset of therapy was a common and benign finding. In conjunction with the reported trials, the IgG levels decreased in the first year of continued therapy. However, the IgA levels did not increase, even after 2 years of therapy.

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Introduction

Bruton tyrosine kinase (BTK), originally described in 1993,[1] is a molecule that acts downstream of B-cell receptors and functions as a key regulator in the maturation of pre-B cells to mature B cells. Bruton's X-linked agammaglobulinemia, first described by Ogden Bruton, is an X-linked recessive genetic disorder caused by mutations in the BTK encoding gene. The result is primary immunodeficiency due to the lack of mature B cells and gammaglobulins.[2] Recently, the oncogenic potential of mutated BTK has been identified in the pathogenesis of B-cell malignancies. Dysregulated BTK activity causes these cancer cells to survive, proliferate, and evade apoptosis. Given its crucial role in the development of B-cell malignancies, an attractive therapeutic strategy to inhibit it was adopted, leading to the development of BTK inhibitors.[3]

Ibrutinib, a first in its class drug, is an irreversible inhibitor that covalently binds to BTK, thereby interrupting the survival and proliferation of malignant B-cell clones. Several clinical trials have demonstrated its durable clinical efficacy and tolerability for various B-cell malignancies.[4] On the basis of the results of a multicenter, single-arm trial involving patients with relapsed or refractory mantle cell lymphoma (MCL),[5] ibrutinib was approved by the Food and Drug Administration (FDA) in November 2013 as second-line therapy. Similarly, with the findings from multicenter, single-arm trials, ibrutinib was approved by the FDA for relapsed and refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in February 2014[6] and for Waldenström macroglobulinemia (WM) in January 2015.[7] More recently, the RESONATE-2 trial randomized treatment-naïve patients with CLL or SLL aged $\geq$ 65 years to receive either ibrutinib or chlorambucil. Ibrutinib was superior to chlorambucil with respect to progression-free survival and overall survival, leading to its approval as a first-line agent for CLL.[8]

Ibrutinib has been designated as a breakthrough drug and has revolutionized the treatment of these B-cell malignancies. In addition to its significant antitumor activity and demonstrated durable clinical efficacy, it is an extremely well-tolerated drug,[5-8] providing a selective advantage over other therapies. Because it is a juvenile drug, ibrutinib is still being investigated in both combinations and head-to-head comparisons with other standard treatments.[4] However, to the best of our knowledge, no studies of this novel drug have been performed in an actual community setting considering the real-world experience. The primary objective of the present study was to determine the clinical efficacy of ibrutinib in various B-cell malignancies.

Byrd et al[9] reported 3-year follow-up data for patients with CLL or SLL receiving continued ibrutinib therapy. According to their analysis, continued therapy not only demonstrated improved durable remissions but also diminished grade $\geq$ 3 adverse effects. An interesting observation was the effect of ibrutinib in restoring humoral immunity. Ibrutinib therapy resulted in an increase or stabilization of IgA levels over time.[9] This effect was further investigated in a study reported by Sun et al.[10] Ibrutinib caused a decrease in IgG levels after 6 months of therapy. However, a sustained increase in IgA levels was observed throughout the follow-up period. Furthermore, the infection rate decreased in these patients, in particular when the increase in serum IgA levels was $>$ 50%.[10]

The secondary objectives in our study included investigating the adverse effects associated with ibrutinib, its effect on the immunoglobulin levels and incidence of peripheral lymphocytosis.

Patients and Methods

Study Approval and Subject Selection

The present study was a retrospective observational cohort analysis conducted at a single institution (Abington Jefferson Health) after approval by the institutional review board. The data from patients with B-cell malignancies, including CLL or SLL, WM, MCL, marginal zone lymphoma, diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma were reviewed. Patients currently receiving ibrutinib or those who had received it in the past since its approval by the FDA for each malignancy were eligible. Treatment naive patients and those who had received previous therapies were included. Patients who had received ibrutinib for $<$ 4 weeks or discontinued the drug within 4 weeks of initiation for any reason were excluded. Forty five patients were identified and selected for the present study.

Data Collection

In addition to the general demographic data, various other variables were recorded, including Eastern Cooperative Oncology Group (ECOG) performance status at treatment initiation, disease stage, previous therapies, therapy duration, hematologic variables, and immunoglobulin levels. The data of the selected patients were de-identified by assigning each patient a unique identification number. The electronic medical records were accessed to collect the data. The response to ibrutinib therapy was determined by the hematologist's clinical assessment and independently using the response criteria for each disease. These included the International Workshop Group on CLL response criteria for CLL, the International Workshop on Waldenström macroglobulinemia version 7 response criteria for WM, and the Lugano criteria for the response assessment in lymphoma. The response was recorded as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). The adverse effects were evaluated and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[11] The number and grade of infections after initiating the drug were also assessed.

Statistical Analysis

Descriptive statistics, including the mean, standard deviation, and median for continuous variables, were used to summarize each of the defined cohorts. To compare the immunoglobulin levels, the Wilcoxon signed rank test was performed, instead of the paired t test owing to the lack of normal distribution. $P = .05$ was determined to indicate statistical significance. The Kaplan-Meier method was used for the time-to-event analysis.

Results

Baseline Disease Characteristics

The total number of subjects selected for the present study was 45 (29 males [64.5%] and 16 females [35.5%]). The median age was 73 years (range, 49-96 years). Most patients (82.2%) were $\geq$ 65 years old. Of the 45 patients, 26 had CLL or SLL, 4 had MCL, 8