Patient-Reported Symptoms During Ibrutinib Holds: A Withdrawal Syndrome

Jorge J. Castillo, Joshua N. Gustine, Kirsten Meid, Toni Dubau, Patricia Severns, and Steven P. Treon

Bing Center for Waldenström’s Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA

Background

The Bruton tyrosine kinase (BTK) inhibitor ibrutinib recently became the first approved therapy for patients with Waldenström macroglobulinemia (WM). The management of ibrutinib-related toxicities, such as bleeding and others, are often managed with temporary interruption of therapy. We observed that some WM patients who held ibrutinib developed symptoms during the time they were holding ibrutinib, which then resolved promptly after ibrutinib reinitiation. Our study aims at describing this “ibrutinib withdrawal” phenomenon.

Patients and Methods

We identified patients seen at our institution between May 2012 and April 2017 who met clinicopathological criteria for WM, met consensus criteria to approved therapy for patients with Waldenström macroglobulinemia (WM). The Bruton tyrosine kinase (BTK) inhibitor ibrutinib recently became the first

Table 1. Characteristics of WM patients who temporarily held and did not hold ibrutinib therapy

Table 2. Clinical characteristics at the time of ibrutinib hold for patients with withdrawal symptoms.

Table 3. Patient-reported symptoms during a temporary ibrutinib hold.

Table 4. Clinical characteristics of WM patients who did and did not develop withdrawal symptoms.

For reprints, please contact jorgej_castillo@dfci.harvard.edu

Results

From the patients who held ibrutinib, 20 (22%) reported withdrawal symptoms. Of these patients who experienced withdrawal symptoms, 17 (85%) were receiving ibrutinib in the relapsed/refractory setting, and 3 (15%) in the frontline setting. All patients were holding ibrutinib for the first time since treatment initiation. The median drug hold length was 7 days (range 3-33 days).

The median time to symptom development was 2 days (range 0-5 days) from the start of the drug hold. Four patients with fever were admitted to the hospital, and after exhaustive workup, no infectious etiology was identified. All patients reported resolution of symptoms, and the same dose of ibrutinib was restarted following the drug hold. Nine patients had subsequent drug holds, and reported the same symptoms during the hold period. Two patients known to develop these symptoms were treated with corticosteroids during holding ibrutinib and resolve rapidly following reinitiation of therapy. We describe patient-reported symptoms that develop in about 20% of WM patients who held ibrutinib and developed symptoms during the time they were holding ibrutinib, which then resolved promptly after ibrutinib reinitiation.

Conclusion

We describe patient-reported symptoms that develop in about 20% of WM patients who held ibrutinib therapy. Such symptoms ensue within 2 days of holding ibrutinib and resolve rapidly following reinitiation of therapy. Clinicians should be aware of this phenomenon which may represent an ibrutinib withdrawal syndrome.