
Successful Management of Ibrutinib-induced Thrombocytopenia with Eltrombopag in a Patient with Waldenström Macroglobulinemia

Abdülkadir Erçalışkan¹, Fatma Zehra Avcı², Ahmet Emre Eşkazan³

¹Division of Hematology, Clinic of Internal Medicine, Düzce Atatürk State Hospital, Düzce, Turkey
²Department of Internal Medicine, Cerrahpaşa Faculty of Medicine, İstanbul University-Cerrahpaşa, İstanbul, Turkey
³Division of Hematology, Department of Internal Medicine, Cerrahpaşa Faculty of Medicine, İstanbul University-Cerrahpaşa, İstanbul, Turkey

Ahmet Emre Eşkazan, Division of Hematology, Department of Internal Medicine, Cerrahpaşa Faculty of Medicine, İstanbul University-Cerrahpaşa, İstanbul, Turkey
emre.eskazan@iuc.edu.tr

7 September 2022
8 November 2022

Keywords: Eltrombopag; ibrutinib; thrombocytopenia; toxicity; Waldenström macroglobulinemia

Ibrutinib is in the therapeutic armamentarium of Waldenström macroglobulinemia (WM) [1], and it is both effective in newly diagnosed [2] and previously treated cases [3]. One of the most common hematological adverse events (AEs) of ibrutinib is thrombocytopenia (32% at all grades) [4], and number of prior therapies are positively correlated with the risk of hematological toxicities [3].

Eltrombopag is a thrombopoietin receptor analog, which is indicated in immune thrombocytopenia and severe aplastic anemia. In addition, eltrombopag can be used in patients with solid tumors experiencing chemotherapy-associated thrombocytopenia [5-7].

Herein we present a heavily pretreated WM case, who was successfully treated with ibrutinib plus eltrombopag combination.

A 61-year-old male was diagnosed with WM in 2009. During the follow-up, he sequentially received chlorambucil, fludarabine, RCD (rituximab + cyclophosphamide + dexamethasone),
BRD (bortezomib + rituximab + dexamethasone), and BR (rituximab + bendamustine) with 2 years rituximab maintenance which was stopped in February 2021. Three months after cessation of therapy, hemoglobin levels dropped to 9 g/dl and IgM levels increased to 2641 mg/dl, and ibrutinib 420 mg/day was initiated in May 2021 due to progressive symptomatic disease. At the treatment start, platelet count was 238 x 10^9/L. But on D7, ibrutinib interrupted due to grade 2 thrombocytopenia (56 x 10^9/L) according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [8]. Platelet counts recovered to 104 x 10^9/L in seven days, and ibrutinib was restarted with a dose of 140 mg. However, after 18 days, grade 3 thrombocytopenia reoccurred (44 x 10^9/L). Since the patient was heavily pretreated, we intend to continue ibrutinib, and eltrombopag 50 mg/day was started on June 18, 2021. Platelet counts remained low after one week and eltrombopag dose was escalated to 75 mg/day. Following 2 weeks of eltrombopag 75 mg/day, platelet counts improved to 105 x10^9/L and ibrutinib 140 mg/day was reinitiated in combination with eltrombopag 75 mg/day.

With this combination, IgM levels dropped from 2641 mg/dl to 1041 mg/dl following 12 months of ibrutinib with complete improvement in clinical symptoms, while platelet counts plateaued over 100 x 10^9/L even after the dose of eltrombopag reduced to 50 mg/day (Figure 1). At this writing, platelet count was 182 x 10^9/L and hemoglobin level was 12.9 g/dl under the combination of 140 mg/day ibrutinib and 50 mg/day eltrombopag in June 2022. Hematological AEs can be clinically significant during ibrutinib therapy, and grade ≥ 3 thrombocytopenia was observed in 11.1% of the cases [9], and dose reduction was performed in 5 patients, while 2 discontinuations were reported due to hematological toxicities. Combination of ibrutinib with eltrombopag resulted in positive results for chemotherapy-associated thrombocytopenia in solid tumors [5-7]. Eltrombopag use was tested in patients with acute myeloid leukemia in combination with induction chemotherapy, however, higher rates of serious AEs and deaths were observed in the eltrombopag arm [10]. In our heavily pretreated patient, since we have used nearly all approved treatment options available in our country, we needed to continue ibrutinib, as grade 3 thrombocytopenia occurred during the lowest possible daily dose. To the best of our knowledge, this is the first report showing eltrombopag use in ibrutinib-induced thrombocytopenia in a WM patient with limited therapy options. In cases with grade 3 ibrutinib-associated thrombocytopenia, thrombopoietin mimetics can be a reasonable treatment modality, especially if ibrutinib therapy is needed to be continued. The use of thrombopoietin mimetics (e.g. eltrombopag) in patients who experience ibrutinib-induced thrombocytopenia can be tested in the future in prospective trials in order to determine to role of this combination among cases with WM.
References


Statements: Informed consent was obtained from the patient.
Figure 1. IgM levels and platelet counts during the course of ibrutinib and eltrombopag combination therapy.