

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

Waldenström Makroglobulinemisi Olan Bir Hastada İbrutinib ile İlişkili Trombositopeninin Eltrombopag ile Başarılı Yönetimi

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## To the Editor,

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

Eltrombopag is a thrombopoietin receptor analog indicated in cases of immune thrombocytopenia and severe aplastic anemia. In addition, eltrombopag can be administered to patients with solid tumors experiencing chemotherapy-associated thrombocytopenia [5,6,7].

Herein we present a heavily pretreated patient with WM who was successfully treated with the combination of ibrutinib plus eltrombopag.

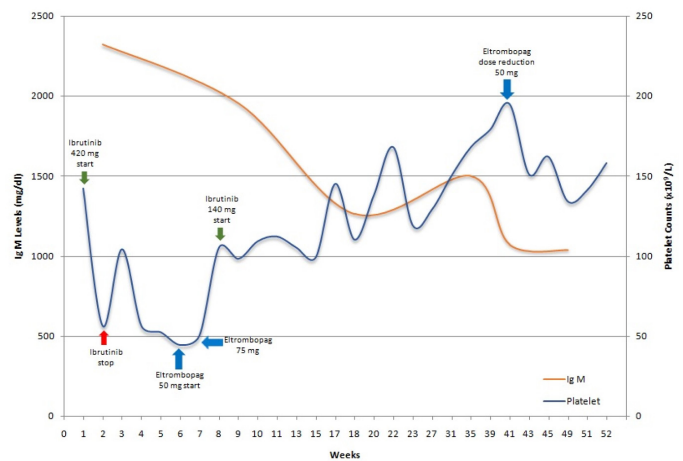
A 61-year-old male was diagnosed with WM in 2009. During follow-up, he sequentially received chlorambucil, fludarabine, RCD (rituximab + cyclophosphamide + dexamethasone), BRD (bortezomib + rituximab + dexamethasone), and BR (rituximab + bendamustine) with 2 years of rituximab maintenance, which was stopped in February 2021.

Three months after the cessation of therapy, his hemoglobin level dropped to 9 g/dL and immunoglobulin M (IgM) level increased to 2641 mg/dL. Ibrutinib was initiated in May 2021 at 420 mg/day due to progressive symptomatic disease. At the start of treatment, his platelet count was  $238 \times 10^9/L$ , but on day 7, ibrutinib was interrupted due to grade 2 thrombocytopenia ( $56 \times 10^9/L$ ) according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [8]. The platelet count recovered to  $104 \times 10^9/L$  in 7 days and ibrutinib was restarted at a dose of 140 mg. However, after 18 days, grade 3 thrombocytopenia reoccurred ( $44 \times 10^9/L$ ). Since the patient was heavily pretreated,

we intended to continue administering ibrutinib, and eltrombopag was started on June 18, 2021, at 50 mg/day. Platelet counts remained low after 1 week and the eltrombopag dose was escalated to 75 mg/day. Following 2 weeks of eltrombopag at 75 mg/day, the platelet count improved to  $105 \times 10^9/L$  and ibrutinib was reinitiated at 140 mg/day in combination with eltrombopag at 75 mg/day.

With this combination, the IgM level dropped from 2641 mg/dL to 1041 mg/dL after 12 months of ibrutinib with complete improvement of clinical symptoms, while the platelet count plateaued over  $100 \times 10^9/L$  even after the dose of eltrombopag was reduced to 50 mg/day (Figure 1). At the time of writing, in June 2022, the platelet count was  $182 \times 10^9/L$  and the hemoglobin level was 12.9 g/dL with administration of ibrutinib at 140 mg/day and eltrombopag at 50 mg/day.

Hematological AEs can be clinically significant during ibrutinib therapy. In a previous study [9], grade  $\geq 3$  thrombocytopenia was



**Figure 1.** Immunoglobulin M (IgM) levels and platelet counts during the course of ibrutinib and eltrombopag combination therapy.

observed in 11.1% of cases and dose reduction was performed for five patients, while two discontinuations were reported due to hematological toxicities.

The combination of ibrutinib with eltrombopag yielded positive results for chemotherapy-associated thrombocytopenia in cases of solid tumors [5,6,7]. 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].

For our heavily pretreated patient, since we had used nearly all approved treatment options available in our country, we needed to continue administering ibrutinib, as grade 3 thrombocytopenia occurred with the lowest possible daily dose. To the best of our knowledge, this is the first report of eltrombopag use in ibrutinib-induced thrombocytopenia in a patient with WM with limited therapy options. In cases of grade 3 ibrutinib-associated thrombocytopenia, thrombopoietin mimetics may be a reasonable treatment modality, especially if ibrutinib therapy needs 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 the role of this combination in cases of WM.

**Keywords:** Eltrombopag, Ibrutinib, Thrombocytopenia, Toxicity, Waldenström macroglobulinemia

**Anahtar Sözcükler:** Eltrombopag, İbrutinib, Trombositopeni, Toksikite, Waldenström makroglobulinemisi

## Ethics

**Informed Consent:** Informed consent was obtained from the patient.

## Authorship Contributions

Concept: A.E., F.Z.A., A.E.E.; Design: A.E., F.Z.A., A.E.E.; Data Collection or Processing: A.E., F.Z.A., A.E.E.; Analysis or Interpretation: A.E., F.Z.A., A.E.E.; Literature Search: A.E., F.Z.A., A.E.E.; Writing: A.E., F.Z.A., A.E.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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