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LETTER TO THE EDITOR

Eltrombopag combined with cyclosporine may have an effect on very severe aplastic anemia

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Dear Editor,

Very severe aplastic anemia (VSAA) is characterized by pancytopenia and marked hypocellular marrow. Standard initial therapy for patients over 35–55 years of age is antithymocyte globulin and cyclosporine A (ATG+CsA) or HLA-matched sibling hematopoietic stem cell transplantation (HSCT).

A previously healthy 48-year-old female presented with a 4-month history of increased symptomatic anemia and 2 weeks of heavy vaginal bleeding. She had no significant family history of hematological disorders. Hematologic parameters met criteria for VSAA, including a bone marrow cellularity of < 20%, an absolute neutrophil count (ANC) of 0.18×10^9/L, a platelet count (PLT) of 4×10^9/L, and a reticulocyte count (Ret) of 14×10^9/L. Flow cytometry showed no evidence of paroxysmal nocturnal hemoglobinuria (PNH). Liver, renal, and thyroid function were normal. Autoimmune antibodies were negative. Viral infections, including HCV, HBV, HIV, EBV, CMV, and B19 virus, were excluded. Bone marrow examination revealed no dysplasia and reticulin stain was positive (fibrosis grade MF-1). BM cytogenetics and FISH analysis were normal. She had no matched sibling donors. Risks and benefits of unrelated HSCT, ATG+CsA and eltrombopag (Epag), and Epag+CsA were discussed with the patient.

This patient was given a combined treatment of CsA and Epag. CsA started at a dose of 5 mg/kg/day, with a target plasma concentration of (200–250) ng/ml. Epag was given at an initial oral dose of 25 mg and increased every 14 days. Hematologic improvements were assessed by the National Institutes of Health (NIH) response criteria for SAA [1]. The erythroid response was observed at a daily eltrombopag dose of 75 mg, 42 days after initiating combined therapy. Neutrophil and platelet responses were observed at day 60. Repeat hematologic evaluation at 5 months showed ANC 1.52×10^9/L, Hb 112 g/L, PLT 64×10^9/L, Ret% 6.2%, and Ret 100×10^9/L. Notably, flow cytometry revealed a new PNH clone with 6% CD59-erythrocytes and 79.7% FLARE-neutrophils. Cytogenetic analysis also showed new cytogenetics abnormalities [45, X, del(X)(p21)] in 10 of 10 metaphase analyses [10]. After 6 months of eltrombopag therapy at a daily dose of 75 mg, both Epag and CsA were discontinued. Peripheral blood counts revealed ANC 2.1×10^9/L, Hb 117 g/L, PLT 99×10^9/L, Ret% 3.2%, and Ret 89×10^9/L. A repeat bone marrow examination showed 40–50% cellularity and unchanged fibrosis grade (MF-1) on reticulin stain. Figure 1 summarizes the hematologic parameters during treatment.

In recent clinical trials, eltrombopag was found to improve trilineage hematopoiesis in patients with SAA refractory to IST [1, 2], and when combined with IST in previously untreated patients, eltrombopag was associated with higher rates of hematologic response than observed historically [3]. Rodgers and Dong et al. [4, 5] also

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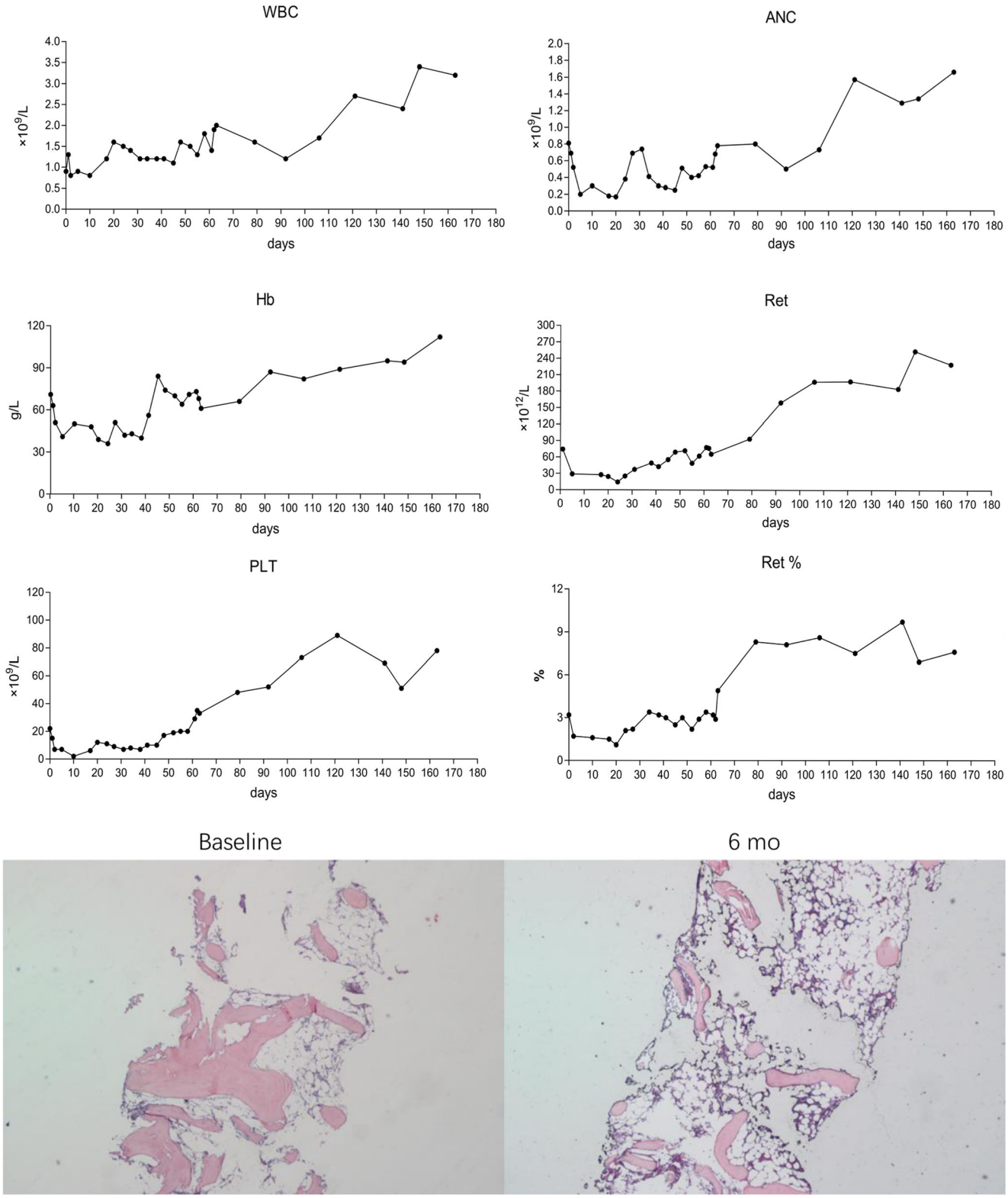

Fig. 1 Hematologic response and bone marrow biopsy at 6 months after combined therapy with cyclosporine and eltrombopag

reported that treatment of SAA patients with CsA combined with Epag can be effective. To our knowledge, this is the first report of trilineage hematologic response in a patient with VSAA treated with Epag/CsA without ATG, suggesting that therapy with eltrombopag may be extended to this patient population as initial therapy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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