Ann Hematol (2011) 90:1357–1359
DOI 10.1007/s00277-011-1180-9

LETTER TO THE EDITOR

Increased requirement for platelet transfusions concurrent with enhanced bleeding during romiplostim treatment in a patient with thrombocytopenia due to bone marrow failure

Ramin Lotfi · Peter Moeller · Mathias Schmid · Hubert Schrezenmeier

Received: 14 January 2011 / Accepted: 31 January 2011 / Published online: 16 February 2011

Dear Editor,

Romiplostim is a thrombopoietic agent. It induces increases in platelet counts in both healthy adults and patients with idiopathic thrombocytopenia (ITP) [1].

At the age of 46 years (Nov. 2003), a female patient was diagnosed with aplastic anemia (AA) showing distinct trilinear bone marrow hypoplasia, specifically of megakaryocytic lineage. Allosensitization against HLA A3, A24, B7, B27 was already present at diagnosis of AA. Six months after triple therapy with cyclosporine A (CSA), corticosteroids, and antithymocyte globulin (ATG) [2], she achieved partial remission with no need for further transfusions for 5 years. CSA medication was stopped after 3 years.

R. Lotfi (✉) · H. Schrezenmeier
Institute for Transfusion Medicine, University of Ulm,
Helmholtzstraße 10,
89081 Ulm, Germany
e-mail: r.lotfi@blutspende.de

R. Lotfi
e-mail: ramin.lotfi@uni-ulm.de

R. Lotfi · H. Schrezenmeier
Institute for Clinical Transfusion Medicine and Immunogenetics Ulm,
German Red Cross Blood Services Baden-Württemberg-Hessen,
Helmholtzstr. 10,
89081 Ulm, Germany

P. Moeller
Institute of Pathology, University of Ulm,
Ulm, Germany

M. Schmid
Department of Internal Medicine III, University Hospital of Ulm,
Ulm, Germany

In August 2008, she became again thrombocytopenic with requirement for transfusional support. At this time, she was diagnosed with amegakaryocytic thrombocytopenia. HLA-matched platelet concentrates (PCs) were given every 10 days with a very good increment of platelet counts (Fig. 1a). Additional alloantibodies against HPA 1b, HLA-A1,3,11,23, 24,66, and HLA-B 7,8,13,27,35,37,38,39,41,44,45,47, 49,50,52,53,55,56,60,61,62,63,73,75,76 occurred in the course of time.

The patient was reluctant to other immunosuppressive regimens. Isolated thrombocytopenia (March 2010, WBC 8.1 K/μL, Hb 14.1 g/dL, platelets 6 K/μL) was not considered as clear-cut indication for allogeneic transplantation. Therefore, we tried an off-label use of romiplastim after informed consent.

Romiplastim (Nplate, AMGEN GmbH Germany) was administered in escalating doses subcutaneously once a week for 4 weeks.

Eighteen days after start of romiplostim, she developed refractoriness to HLA- and HPA-matched PCs with distinct signs of bleeding in terms of generalized petechiae combined with mucosal hemorrhage leading to pharyngeal congestion (Fig. 1b) and macrohematuria (Fig. 1a and c). Treatment with ε-aminocapronate was of very temporary limited value. She needed matched PCs every 24 to 48 h due to active bleeding. Post-transfusional increment of platelet count dropped back to levels around 10 K/μL within 2 h after transfusion. Besides significantly shortened survival of transfused platelets (Fig. 1a and c), their functionality was strongly impaired given that before romiplostim treatment, the patient had presented much less clinical signs of bleeding with similar pre-transfusional platelet counts. Due to thrombocytopenia, it was not possible to prove impaired platelet functionality in vitro.

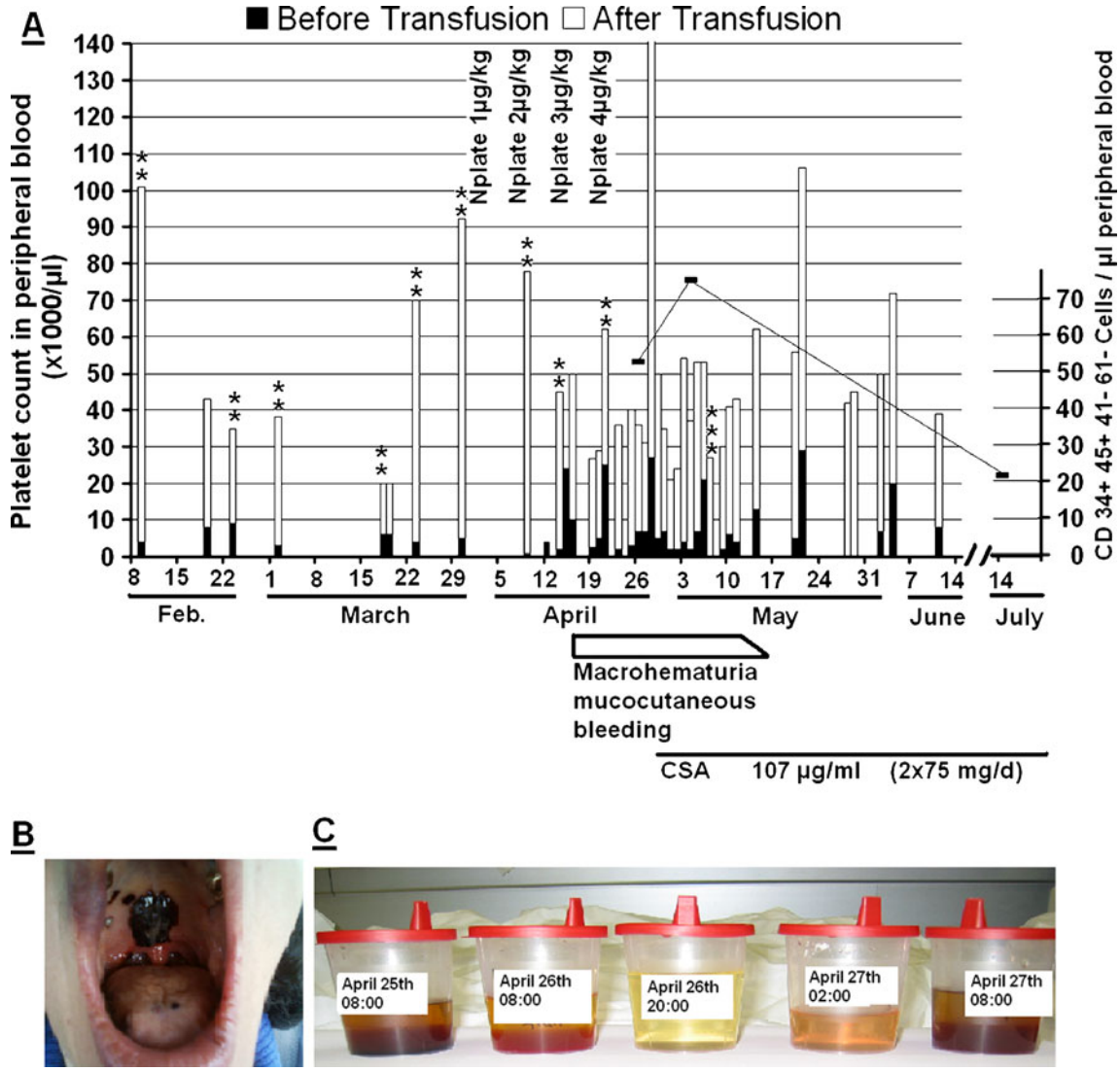

Fig. 1 **a** Increased need for platelet transfusions with shortened shelf life of platelets. Shown is patient's platelet count before (*black*) and after transfusion (*open bars*) of HLA-matched PCs. One PC-unit with around 3×10^{11} platelets/unit was transfused on the indicated days, otherwise, *asterisks* show number of transfused PCs on the indicated day. Romiplostim was given once a week in escalating doses as indicated. Cyclosporin A (CSA) was given during the indicated time period. **b** Mucosal hemorrhage following romiplostim-induced autoimmune thrombocytopenia. About 2 weeks after the beginning of treatment with romiplostim, the patient developed severe signs of bleeding with mucosal hemorrhage leading to pharyngeal congestion. **c** Macrohematuria after the second week of treatment with romiplostim. The patient was transfused with one HLA-matched PC on April 26 with an increment from 7,000 to 29,000 platelets μL^{-1}. Short half life of transfused platelets with subsequent recurrence of macrohematuria can be assessed within hours after transfusion

Circulating blasts (up to 2%) and increasing number of CD34+45+41−61− cells (up to 75/µL) emerged in peripheral blood. Hypersplenism, paroxysmal nocturnal hemoglobulinuria (flow cytometric analysis for clonal loss of CD 55 and CD 59 expression), and hemophagocytic syndrome (bone marrow cytology and histology) as possible causes could be ruled out. Bone marrow aspirates showed a normal karyotype, while the histologic/cytologic assessment was consistent with a myelodysplastic syndrome (MDS) (subtype refractory cytopenia with multilineage dysplasia).

Three weeks after stopping romiplostim, we noticed a significant regression of signs of bleeding concurrent with a better post-transfusional platelet increment. Twelve weeks after cessation of romiplostim, we could still find 22 CD34+ cells/µL peripheral blood.

Significantly shortened survival of transfused HLA- and HPA-matched platelets combined with impaired functionality in timely association with romiplostin treatment and in particular, the reversibility after cessation of romiplostin supports the hypothesis that romiplostim in this case might have induced both increased consumption and functional impairment of platelets. The mechanism for this effect remains unclear. Notably, an increased number of circulating progenitor cells (CD45+34+), which were

negative for megakaryocyte/platelet markers CD41 and CD61, were observed suggesting a mobilizing effect of romiplostin.

The bone marrow aspirate after romiplostim treatment was compatible with MDS. This is most likely due to natural evolution of AA to MDS which occurs at increased frequency in follow-up after AA [3].

From this case, we cannot proof a causal relationship between the romiplostim treatment and the described adverse effect; however, the close timely association between start/stop of romiplostim treatment and onset/disappearance of enhanced signs of bleeding and higher need for transfusions is highly suggestive of a romiplostim adverse effect. This case should prompt careful clinical observation of other cases of romiplostim treatment for indications other than ITP, in particular, in transfusion-dependent bone marrow failure syndromes.

References

1. Broudy VC, Lin NL (2004) AMG531 stimulates megakaryopoiesis in vitro by binding to Mpl. Cytokine 25(2):52–60
2. Frickhofen N, Heimpel H, Kaltwasser JP, Schrezenmeier H (2003) Antithymocyte globulin with or without cyclosporin A: 11-year follow-up of a randomized trial comparing treatments of aplastic anemia. Blood 101(4):1236–1242
3. Socie G, Mary JY, Schrezenmeier H, Marsh J, Bacigalupo A, Locasciulli A et al (2007) Granulocyte-stimulating factor and severe aplastic anemia: a survey by the European Group for Blood and Marrow Transplantation (EBMT). Blood 109(7):2794–2796