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Subcutaneous bortezomib is highly effective for pure red cell aplasia after ABO-incompatible haematopoietic stem cell transplantation

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Dear Sir,

Pure red cell aplasia (PRCA) is an uncommon complication of ABO-incompatible haematopoietic stem cell transplantation. It is characterised by anaemia, reticulocytopenia and absence of erythroid precursors in a morphologically normal-appearing bone marrow (Sawada *et al.*, 2009). Most cases of PRCA resolve spontaneously within weeks to months. While a small subset of patients has a protracted disease course requiring continued red blood cell (RBC) transfusions, there is no approved standard of care for PRCA. Tapering of immunosuppressives (including steroids and calcineurin inhibitors), plasma exchange, rituximab and anti-thymocyte globulin have all been employed with varying success rates (Booth *et al.*, 2013). Here we describe a case of PRCA after ABO-incompatible transplant that responded remarkably to treatment with subcutaneous administration of the proteasome inhibitor bortezomib.

A 60-year old woman received a non-myeloablative, human leucocyte antigen (HLA)-matched, ABO-mismatched sibling donor transplant for lenalidomide-refractory myelodysplastic syndrome (5q–). She received fludarabine/busulfan conditioning and tacrolimus/methotrexate for graft versus host disease (GVHD) prophylaxis. The donor was blood type A Rh-positive, and the recipient was O Rh-positive. The patient's post-transplant course was complicated by delayed engraftment, thrombocytopenia and autoimmune haemolytic anaemia. She received pentostatin 4mg/m² and donor lymphocyte infusion (DLI) for delayed engraftment on day 100. When seen at our institution 22 months post-transplant, she had transfusion-dependent anaemia (requiring RBC transfusions every 2–3 weeks) and reticulocytopenia. Bone marrow biopsy showed erythroid aplasia and preserved haematopoiesis in other cell lines; dysplasia was absent, and parvovirus testing was negative. The patient had evidence of complete engraftment based on short tandem repeat analysis with 95–100% donor DNA in CD3 positive peripheral blood cells as well as bone

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CONFLICT OF INTEREST

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marrow. Blood typing reflected transfused type O Rh-negative RBCs. Neither type A cells from the donor or Rh-positive cells from the patient were detected using either manual test tube or automated solid phase (Galileo Echo, Immucor, Norcross, GA, USA) methods, and reactions for anti-A and anti-B were 4+. The direct anti-globulin test (DAT) was negative using a saline test tube method with murine monoclonal antibodies for IgG and C3d (Immucor). The patient had a history of anti-S, -C and -K, an unidentified antibody, and autologous anti-D. At presentation to our institution the antibody screening was negative, though an unidentified antibody was subsequently detected. Anti-A and anti-B titres were performed using A₁ and B cells (Immucor) and a gel card system [buffered gel and anti-human globulin anti-IgG (Rabbit), ID-Micro Typing System, Micro Typing Systems Inc., Pompano Beach, FL, USA]. High titres of anti-A (IgG 512 and IgM 32) and anti-B (IgG 256 and IgM 32) isohaemagglutinins were detected. Isohaemagglutinin titres remained elevated despite transfusion with washed RBCs to reduce passive transfer of an anti-A. She was treated with prednisone 60mg/day, rituximab 375mg/m² weekly four times and methylprednisolone 1 g weekly six times without response. Eventually, all immunosuppressive medications were discontinued to induce a graft vs recipient response. Two subsequent bone marrow biopsies continued to show nearly absent erythropoiesis, and the rare erythroid cells present lacked the blood group A antigen (Fig 1a–c). Anti-A and anti-B titres remained elevated so, therefore, PRCA was thought to be due to the recipient's plasma cells making anti-A antibodies. Therapy was changed to more effectively target plasma cells. Bortezomib is a potent inducer of apoptosis in plasma cells, and therapy was initiated by administering subcutaneous bortezomib 1.3mg/m² weekly four times. The patient responded remarkably well to therapy. A month after completion of bortezomib, the patient's haemoglobin measured 12.1 g/dL, reticulocyte count was $174 \times 10^9/L$ and IgM and IgG anti-A titres were both <1. Bone marrow biopsy showed relative erythroid hyperplasia, and the majority of the erythroid precursors expressed the blood group A antigen (Fig 1d–f). The patient continues to do well, and at the time of her most recent evaluation, her haemoglobin was 13.9 g/dL. She has remained transfusion-independent. For the past 3 months, the patient has been requiring phlebotomies every 2 weeks due to transfusion-related iron overload.

PRCA after major ABO-incompatible transplant is thought to be caused by persistence of recipient plasma cells that continue to secrete anti-donor isohaemagglutinins (Griffith *et al.*, 2005). As in this case, antibody titres may remain elevated for a longer duration in patients receiving non-myeloablative preparatory regimens (titres remained elevated for greater than 2 years post-transplant in this patient). Bortezomib is a proteasome inhibitor that selectively induces apoptosis in plasma cells, and it has been used successfully to treat antibody-mediated rejection in both renal and liver transplant patients (Westphal *et al.*, 2013). A case of PRCA following ABO-mismatched haematopoietic transplant that was successfully treated with intravenous (IV) bortezomib has also been reported (Poon and Koh, 2012). Our case demonstrates that subcutaneous bortezomib may also be effective in treating this entity. The lack of long-term follow-up data in our case precludes any assessment about the durability and persistence of response to bortezomib; however, we conclude that subcutaneous bortezomib may be an effective treatment for patients with PRCA mediated by residual host isohaemagglutinins after ABO-incompatible haematopoietic transplantation.

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Fig. 1.

(a–c) Bone marrow biopsy, prior to bortezomib therapy. (a) Wright–Giemsa stained smear, 50× oil, note that only rare erythroid cells are present (arrow). (b) Haematoxylin and eosin (H&E) stained trephine section, 20×. The marrow is normocellular, with a marked relative erythroid hypoplasia. Red cell precursors are rare to absent, confirmed by a glycophorin A immunostain (not shown). (c) Blood group A immunostain, 20× – the stain highlights rare megakaryocytes, but a majority of cells lack this antigen. (d–f) Bone marrow biopsy, after bortezomib therapy. (d) Wright–Giemsa stained smear, 50× oil, note that there are numerous nucleated red blood cells. (e) H&E stained trephine section, 20×. The marrow is hypercellular, and there are numerous erythroid islands (red circle). (f) Blood group A immunostain, 50× – there are numerous red cells present that express blood group A. The erythroid islands are composed of nucleated red cells, which are dark staining. The lighter staining cells are non-nucleated red cells that also express this antigen.