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Pulsed-high-dose dexamethasone as a treatment for pure red cell aplasia following ABO-incompatible allogeneic stem cell transplantation

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Dear Sir,

Owing to the limitations of donor availability, about 30–50% of allogeneic haematopoietic stem cell transplantations (HSCTs) are carried out between blood type A, B or O (ABO)-mismatched donors and recipients (Mielcarek *et al.*, 2000). No consistent evidence has been found to indicate that ABO-incompatibility will adversely affect neutrophil and platelet engraftment, graft vs host disease (GvHD) severity, the relapse rate of disease, the non-relapse mortality rate and overall survival, presumably due to the lack of ABO antigen expression during the early stages of haematopoiesis (Rowley *et al.*, 2011). However, clinical complications such as instant/delayed hemolysis, delayed erythroid engraftment and pure red cell aplasia (PRCA) do occur as a result of ABO antigen disparity (Yazer & Triulzi, 2007). About 10–20% of ABO-mismatched HSCT recipients suffer from PRCA and become red cell transfusion-dependent (Mehta *et al.*, 1996). As this rare complication resolves itself spontaneously in some patients, others need more aggressive treatment to manage the condition. Here, we report a case in which prolonged PRCA after an ABO-incompatible allogeneic HSCT was successfully treated using a short course of four pulses of high-dose steroids.

A 39-year-old male was admitted in October 2009 with pancytopenia [white blood cells (WBC): $3820 \mu\text{L}^{-1}$, absolute neutrophil count (ANC): $306 \mu\text{L}^{-1}$, haematocrit: 30%, platelet: $18 \times 10^3 \mu\text{L}^{-1}$] and circulating blasts (50%). Bone marrow biopsy revealed a 40% cellular bone marrow with sheets of blasts (>95%) and absence of trilineage haematopoiesis. Flow cytometry studies revealed acute myeloid leukaemia (AML), positive of CD34 and CD117. Cytogenetic analysis revealed a complex karyotype: $-8, \text{der}(2)\text{t}(1;2)(\text{q}21;\text{q}34), \text{der}(16)\text{t}(8;16)(\text{q}11.2;\text{q}11.2)$. The patient underwent induction therapy using cytarabine, daunorubicin and etoposide, and achieved a complete remission with restoration of normal peripheral counts. The only available donor identified for allogeneic HSCT was matched for human leukocyte antigen (HLA)-A, B, Cw, DRB1, DRB5 and DQB1 allele groups, but was mismatched for one DRB3 allele and two DRB1 alleles. The patient's blood type was O+ whereas the donor was A+. Peripheral blood stem cells (PBSCs) were mobilised by granulocyte colony-

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CONFLICT OF INTEREST

The authors have no competing interests.

stimulating factor (G-CSF) administration and collected from the donor for transplantation. After administration of a myeloablative preparative regimen of busulfan and cyclophosphamide, 265.2×10^6 CD34+ cells were infused into the recipient on 31 March 2010. GVHD prophylaxis consisted of tacrolimus and mycophenolate. Sixty days after infusion of stem cells, a bone marrow biopsy revealed a hypocellular marrow (20–30%) with myeloid predominance (Myeloid : Erythroid = 8 : 1) and no detectable leukaemia. Microsatellite polymerase chain reaction (PCR) revealed 100% chimerism of donor cells within the marrow. By 100 days post-transplant, the peripheral counts were WBC 8020 (per μL), ANC 4160 (per μL) and platelets $205 (\times 10^3 \mu\text{L}^{-1})$. However, the patient remained red cell transfusion-dependent, with an inappropriately low reticulocyte count and no signs of hemolysis detected. Ninety days post-transplant, the patient developed grade I stage II GvHD of the skin that was not treated other than with continuation of tacrolimus. A bone marrow aspirate at 180 days revealed a hypocellular marrow (10%) with normal megakaryocytes and a full range of myeloid maturation, but a near absence of erythroid progenitors. Tacrolimus was tapered off and stopped on day 347, with resolution of the skin GVHD, and a repeat bone marrow biopsy on day 361 again showed a near absence of erythroid precursors, consistent with PRCA. Erythropoietin (EPO) level was markedly elevated at 640 mIU mL^{-1} (normal 4.1–19.5). Transfusion dependence persisted (Fig. 1), and immunoglobulin 1 g kg^{-1} was intravenously administered on day 430 post-transplant without alleviation of the transfusion dependence. An anti-A isohemagglutinin test on day 578 revealed a titer of 1 : 32 (Fig. 1). Since the patient was not transfused with anything other than blood type A products, and the last intravenous immunoglobulin (IVIG) he got was more than 6 months ago, it was believed that the anti-A antibody was derived from the major ABO-incompatibility. On that day he received a red cell transfusion for a haematocrit of 18.6% and was then initiated on a course of dexamethasone (Decadron: 40 mg day^{-1} on days 1–4, 9–12 and 17–20) (Fig. 1). From that day onward, no further transfusions were needed. His haematocrit rose above 30% toward the end of the dexamethasone treatment. Circulating reticulocytes rose from nearly absent to 3.7%. On day 711 his anti-A titer had dropped to an undetectable level (1 : 1). By the time of writing this report, the patient has been 32 months free of red blood cell (RBC) transfusion and asymptomatic.

PRCA occurs infrequently even in ABO-incompatible HSCT, and the specific mechanism underlying this complication remains unknown. It has been proposed that the antibodies against donor RBC secreted by residual recipient B cells or plasma cells might be responsible, and particularly when the donor blood type is A (because of the high affinity between A antigens and anti-A antibodies, and the higher expression density of A antigens on the cell surface than B) (Lee *et al.*, 2000). A number of treatment modalities have been tried for PRCA (Rowley *et al.*, 2011), including steroids (Yang & Hsu, 2001; Deotare *et al.*, 2006), EPO, plasmapheresis, immunoadsorption, donor lymphocyte infusion (DLI), rituximab and bortezomib (Khan *et al.*, 2014).

There have been relatively few cases reported in the literature in which high-dose steroids have been used as monotherapy to treat both idiopathic PRCA (Ozsoylu, 1990) and ABO-incompatible-HSCT-related PRCA (Yang & Hsu, 2001; Deotare *et al.*, 2006). In one case report of post-transplant PRCA, the authors claimed that adequate dosage and duration of

prednisolone were essential in eliciting a meaningful clinical response (Yang & Hsu, 2001). These authors had also correlated the increasing dosage of steroids with the decreasing titering of anti-donor isohemagglutinins, implying the therapeutic mechanism of high-dose steroid by suppressing anti-donor antibody (Yang & Hsu, 2001; Deotare *et al.*, 2006), which also corroborated the theory of identifying the isoagglutinin level as a risk factor of PRCA in ABO-incompatible HSCT (Lee *et al.*, 2000). Particularly, high-dose dexamethasone was used in one case of PRCA after a ABO-mismatched-HLA-matched sibling donor peripheral blood stem cell transplantation (PBSCT) (Deotare *et al.*, 2006). The patient suffered a yearlong post-transplant PRCA, which was resistant to oral prednisone, rituximab, EPO and reduced cyclosporine treatments. A single dosage of dexamethasone (40 mg, i.v. for 4 days) was administered on day 348 and the PRCA was resolved 40 days afterwards. It was claimed that the regimen was adopted and modified from the treatment of chronic idiopathic thrombocytopenic purpura (ITP).

However, there are several points of significance in our case that are worthy of notice. First, our patient suffered from a high-risk AML with complicated karyotype cytogenetics. With a potentially poor prognosis, the only HSCT donor that could be found was an unrelated one with three mismatch HLA alleles for PBSC transplantation. Second, the high intrinsic EPO level (640 mIU mL^{-1}), the prolonged period of anaemia (600 days) and unresponsiveness to IVIG treatment implicated that the anti-A antibodies against donor targeted cells at a very early stage of RBC formation and the PRCA was a tough and refractory one. The long duration of post-transplant PRCA reflected the lifespan of the residual plasma cells producing the antibody (Volin & Ruutu, 1990). Thus, we presumed that by simply reducing of the anti-A antibody level with oral prednisone or a single dosage of dexamethasone, the treatment might not work that well in our case. Rather, we modelled our therapy after the treatment of multiple myeloma using several pulses of high-dose dexamethasone, believing that directly targeting and eradicating the residual host plasma cells would be of better clinical benefit. High-dose dexamethasone was incorporated into vincristine and doxorubicin as a standard regimen for multiple myeloma treatment (Alexanian *et al.*, 1986). Thus, we used the same dexamethasone regimen here in treating HSCT-associated PRCA, aimed at eliminating the plasma cells producing the anti-donor antibodies. After four courses of Decadron, the isohemagglutinin test showed that the patient anti-A titer had dropped to an undetectable level (1 : 1), unlike the previously reported result of single dose dexamethasone (1 : 2 IgM, 1 : 2 IgG) (Deotare *et al.*, 2006). Based on our experience as well as previously reported cases, we recommend that pulsed-high-dose steroids be considered as a first line therapy in the management of PRCA that develops following ABO-incompatible allogeneic HSCT.

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Fig. 1.
Laboratory parameters. Hematocrit values and anti-A titers plotted over time in relation to the different interventions used in this case.