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Pre-transplant reduction of isohaemagglutinin titres by donor group plasma infusion does not reduce the incidence of pure red cell aplasia in major ABO-mismatched transplants

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Summary:

Major ABO incompatibility in stem cell transplant recipients has been associated with pure red cell aplasia (PRCA). Reduction of incompatible isohaemagglutinin titres pre-transplant by various methods has been thought to reduce the incidence of PRCA. Our data suggest that pre-transplant reduction of incompatible isohaemagglutinin titres by donor group plasma infusion does not reduce the incidence of PRCA. We also failed to find any relationship between pre-transplant ABO isohaemagglutinin titre and the risk of developing PRCA.
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The ABO blood group system is of critical importance in transfusion medicine, but has a less dramatic impact on haematopoietic transplantation.[1,2] ABO antigens are potently immunogenic and are expressed on multiple tissues in addition to red blood cells.[3] Since ABO and human leukocyte antigens (HLA) are inherited independently, ABO incompatibility may occur in 20–40% of HLA-matched allogeneic haematopoietic stem cell transplants (SCT).[2] Graft failure does not occur with increased frequency, and most studies indicate that the incidence of graft-versus-host disease (GVHD) is not increased following ABO-incompatible transplants.[2,4–6]

Major ABO incompatibility in SCTs, defined as incompatibility of donor ABO antigens with the recipient's immune system, has been associated with pure red cell aplasia (PRCA) following conventional myeloablative conditioning.[7–11] The proposed risks for PRCA in this setting include the use of cyclosporine (CsA) as GVHD prophylaxis,[7,8] high initial or persistently elevated host antidonor isohaemagglutinin levels,[7,10] and RBC incompatibility involving donor A antigens.[10,11] Reduction of incompatible isohaemagglutinin titres prior to transplant, either by plasma exchange, immunoadsorption or donor-type RBC infusion, has been utilized in the past.[2–14] However, this practice has been highly variable and there are no specific recommendations. In addition, limited data suggest that this reduction in pre-transplant titres also reduces the incidence of PRCA.[15]

We have been using a relatively unusual and rarely reported form of isoagglutinin reduction for major ABO-mismatched SCTs. Donor group plasma is infused prior to transplant in order to reduce the incompatible titres in ABO-mismatched transplants, in addition to RBC depletion to prevent severe hemolytic reaction at the time of marrow transfusion.[12,16–21] Hence, we carried out a retrospective analysis to determine whether the reduction in titres reduced the incidence of PRCA.

Patients and methods

We undertook a retrospective analysis to study the incidence of PRCA in 357 patients who had undergone 372 allogeneic transplants between 1986 and 2003 at our centre. Of these, 83 were major ABO-mismatched transplants. The bone marrow harvest was RBC depleted in all patients who underwent bone marrow transplantation (BMT) in contrast to patients who underwent peripheral blood stem cell transplantation (PBSCT), where no such manipulation of the graft was undertaken. RBC depletion was carried out using hydroxyethyl starch sedimentation or apheresis.[22–24] Red cell volumes post RBC depletion were not documented. All recipients with incompatible isohaemagglutinin titres above 1:64 were infused with donor group plasma at a dose of 10–15 ml/kg/day for 4 days prior to transplant in order to reduce the incompatible titres. Incompatible titres were monitored pre-transplant and post-infusion of donor group plasma. Titres were estimated by saline agglutination and the indirect antiglobulin test (IAT) using the same assay system. PRCA was defined as the presence of delayed RBC recovery with a reticulocyte count below 1%, after neutrophil and platelet engraftment, defined as an absolute neutrophil count $>500/mm^3$ and an

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unsupported platelet count $>20\,000/mm^3$. Bone marrow examination was undertaken in the initial few patients to document PRCA, but a falling haemoglobin with a low reticulocyte count and normal white cell and platelet counts with complete donor chimerism, in the setting of an ABO-mismatched transplant, were considered adequate for the diagnosis of PRCA.

Results

Between 1986 and 2003 there were 83 (22%) major ABO-mismatched transplants at our centre. There were 53 males (64%) and 30 females (36%) with an average age of 18.5 years (range: 3–51). There were 70 (84%) bone marrow (BM) and 13 (16%) peripheral blood stem cell (PBSC) transplants. The bone marrow harvest was RBC depleted in all patients. In all, 54 patients with baseline titres greater than 1:64 were given donor group plasma at a mean dose of 45 ml/kg (range: 12–128). There were no reactions to donor group plasma infusion in any patient. One patient developed intravascular haemolysis on the day of marrow infusion, but recovered with hydration and steroids.

PRCA developed in 15/83 patients (18%) at a mean duration of 61 days post-transplant (range: 40–95), and lasted for a mean duration of 3.6 months (range: 1–12). There were eight males and seven females with an average age of 22 years (range 5–51). The harvest was bone marrow in 10 and peripheral blood stem cells in five. The median major saline agglutination and IAT-incompatible titres were 1:128 (range: 2–512) and 1:512 (range: 4–2048) in the PRCA group when compared to 1:128 (range: 4–1024) and 1:256 (range: 16–2048) in the non-PRCA group. The reduction in the saline agglutination and IAT titres after infusion of donor group plasma was by two dilutions to 1:32 (range 2–128) and one dilution to 1:256 (range 4–1024) in the PRCA group. In comparison, in the non-PRCA group, the reduction in titres was similar by two dilutions to 1:32 (range 2–1024) and one dilution to 1:128 (range 4–2048). In all, 45/68 patients (66%) had received donor group plasma to reduce incompatible titres in the non-PRCA group, while 9/15 patients (60%) received donor group plasma in the PRCA group. This difference was not statistically significant. The average volume of incompatible plasma infused was 47 ml/kg (range: 21–70) in the PRCA group and 44 ml/kg (range: 12–128) in the non-PRCA group (Table 1). Out of the 15 patients who developed PRCA, 12 were treated with prednisolone for a mean duration of 4.4 months (range: 1–9) in addition to CsA. Prednisolone was added in patients who developed PRCA while taking CsA. The average units of RBC transfused were 3.6 (range: 1–9). The time of initiation of RBC transfusion ranged from 1.5 to 3 months, with a mean of 2 months post-transplant. The mean time to recovery was 3.5 months, with a maximum of 12 months. All patients have recovered from PRCA. The incidence of PRCA was higher in the PBSC group when compared to the BM group, but this was not statistically significant ($P=0.057$) using the χ^2 test (Table 2). We found no relationship between pre-transplant isohaemagglutinin titre and the risk of developing PRCA (Table 3).

Table 1 Patient characteristics

	PRCA (n = 15)	*Non-PRCA (n = 68)*
Baseline saline agglutination titre	1:128 (2–512)	1:128 (4–1024)
Baseline IAT titre	1:512 (4–2048)	1:256 (16–2048)
No. received plasma	9/15 (60%)	45/68 (66%)
Volume of plasma (ml/kg)	47 (21–70)	44 (12–128)
Post-plasma infusion saline agglutination titre	1:32 (2–1024)	1:32 (2–1024)
Post-plasma infusion IAT titre	1:256 (4–1024)	1:128 (4–2048)

Table 2 PRCA by source of stem cells

	BM = 70	*PBSC = 13*
PRCA* (15)	10 (14.3%)	5 (38.4%)
Received plasma (9)	7/10	2/5
Non-PRCA (68)	60	8
Received plasma (45)	42/60	3/8

*$P=0.057$.

Table 3 Antibody titres and incidence of PRCA (pre infusion of plasma)

Antibody titres	*Number of patients*	*No. with PRCA incidence and %*	*P-value*
Titres $\leqslant$1:128	38	6 (15.7%)	0.61 NS
Titres $>$1:128	45	9 (20%)	
Titres $\leqslant$1:64	19	5 (26.3%)	0.28 NS
Titres $>$1:64	64	10 (15.6%)	
Titres $\leqslant$1:32	11	1 (9.1%)	0.40 NS
Titres $>$1:32	72	14 (19.4%)	

Discussion

Our observations differ from previous reports which, although controversial, hold that reduction of antidonor isoagglutinin levels in the recipient seems to enhance engraftment of RBC precursors. Furthermore, there are no studies directly comparing the policies of reducing incompatible titres *vs* not reducing them, pre-transplant. Analysis of data in this series shows that the development of PRCA is not related to pre-transplant isohaemagglutinin levels. In our centre, all patients undergoing major ABO-mismatched BMT or PBSCT received donor group plasma if the titres were greater than 1:64. This policy does not, however, seem to have made any difference to the incidence of PRCA. This is in contrast to the data reported earlier that the policy of reducing incompatible titres resulted in a zero incidence of PRCA. We conclude that pre-transplant incompatible isohaemagglutinin titres do not correlate with PRCA post-transplant, nor does reduction of these titres with incompatible plasma make any difference to the incidence of PRCA. The graft source, whether PBSC or bone marrow, does not have any effect on the risk of developing PRCA in ABO-incompatible transplantation.

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