ACTA MÉDICA PORTUGUESA 1994; 7: 21-24

BONE MARROW TRANSPLANTATION WITH MAJOR ABO INCOMPATIBILITY.

Experience of the Bone Marrow Transplantation Unit - Francisco Gentil Portuguese Institute of Oncology, Lisbon Centre

RUI COELHO, ISABEL CUNHA, INÊS NOLASCO, ALEXANDRA MACHADO, MANUEL ABECASSIS

Santa Maria Hospital Immuno-Hemotherapy Department. Egas Moniz Hospital Immuno-Hemotherapy Department, Bone Marrow Transplantation Unit - Francisco Gentil Portuguese Oncology Institute, Lisbon Centre.

SUMMARY

Thirteen patients submitted to bone marrow transplantation (BMT), HLA A and B identical, with mixed negative lymphocyte culture and major ABO incompatibility were retrospectively evaluated. Gravity sedimentation by hydroxyethyl starch was used in almost all cases to deplete erythrocytes from bone marrow (12/13): a removal rate of 90% - corresponding to an erythrocyte residual volume of 27,4 rate ml - and a nucleated cell recovery of 76% (mean values) were obtained. All patients underwent a hyperhydration regimen and received corticosteroid prophylaxis before bone marrow infusion. Considering the most important immunohematological problems associated to this type of transplant, we verified that seven patients developed minor complications and among them only one had long term consequences. In comparison with the control group, ABO identical and with minor incompatibility, the study group had delayed onset of erythropoiesis and needed greater erythrocyte tranfusion support. We concluded that major ABO incompatibility does not constitute a drawback to BMT success in most patients.

INTRODUCTION

Initially considered as a counterindication to bone marrow transplantation (B.M.T.), major ABO incompatibility later revealed itself as a problem that could be solved by the removal of ABO antibodies in the receiver and/or the depletion of bone marrow (B.M.) erythrocytes. Despite this the increase in antibody rebound, in the first case, and the residual erythrocyte volume, in the second, justify the occurrence of adverse effects such as hemolysis, the persistence of agglutinines and the delay in erythropoesis onset.

This type of transplantation does not have a greater incidence of graft rejection nor does it present a reduced patient survival on comparing them with those who received identical ABO B.M. or B.M. with minor ABO incompatibility.

Despite the casuistics still being low we decided to assess, retrospectively, the first thirteen transplanted patients with major ABO incompatibility - in comparison with the remaining patients - in what concerns the three above mentioned parameters, transfusion therapy and B.M. erythrocyte depletion by Hydroxiethyl Starch (H.E.S.).

METHODS

PATIENTS

The files of the thirteen patients (eight male and five female) submitted to identical HLA A and B B.M.T., with negative mixed lymphocyte culture (M.L.C.) and major ABO blood type incompatibility were consulted. These patients received 13 B.M.T. and 2 Cell Reinforcements (infusion of medullar cells of the same donor without conditioning) during the period between May 1987 and October 1990. The respective diagnoses are indicated in *Table 1*.

Received for publication: 1 August, 1991

Table 1 – Patients submitted to B.M.T. with major ABO blood group incompatibility

		ABO and RH Groups	
UPN	**Diagnosis**	**Receiver**	**Donor**
06	AA	O -	A +
12	AML	O +	A +
22	MDS	A +	B +
23	ALL	O +	B +
25	CML	O +	B +
27	ALL	A +	B +
31	MM	B +	A +
35	ALL	A +	B +
39	LL	O +	A +
41	CML	O +	A +
43	CML	O +	A -
45	CML	A +	B +
50	AML	A +	B +

UPN - Unique Patient Number; AA - Aplastic Anemia; ALL - Acute Lymphoblastic Leukemia; CML - Chronic Myeloid Leukemia; AML - Acute Myeloblastic Leukemia; MDS - Myelodisplastic Syndrome; LL - Lymphoblastic Lymphoma; MM - Multiple Myeloma

The conditioning regimen comprised cyclophosphamide (CPP) associated to busulphan (Bu) or total body irradiation (TBI), except in patient UPN 6 who was prepared only with CPP. The prophylaxis of graft versus host disease (G.V.H.D.) always included cyclosporine. All patients were put on a regimen of hyperhydration 24 hours before the B.M.T.- 3.000 cc of 5% dextrose in saline solution per m^2 of body surface and infusion of 50 cc of 20% hypertonic manitol - and received 125 mg of succinic methylprednisolone intravenously 1 hour before B.M. infusion. Blood groups ABO and RH of the receivers and respective donors of B.M. are described in *Table 1*. The thirty-seven patients subjected to B.M.T. in the same period of time, identical A and B HLA with negative M.L.C. and without ABO incompatibility or with minor incompatibility, were considered the control group.

STUDY METHODOLOGY

1. Erythrocyte depletion by HES - By using the HES sedimentation technique described by Dinsmore, we calculated the percentage of erythrocyte removal, the residual volume of erythrocytes and the recovery percentage of nucleated cells in twelve B.M. (11 B.M.T. and 1 Cell Reinforcement).

Two patients, whose B.M. was processed in the Haemonetics H-30 discontinuous flux cell separator, are not included in this analysis (UPN 22 and UPN 45).

2. Occurrence of acute and/or late hemolysis – We verified the occurrence of hemolysis according to the classic clinical and laboratory parameters (hemoglobin, bilirubin, LDH, etc).

3. Hematopoesis onset – We assessed both groups taking into consideration the day after transplantation in which neutrophil counts were above or the same as 500/l, platelets above or the same as 25.000/l and reticulocytes above 1%.

4. Agglutinine persistence – We registered the number of days after transplantation in which ABO agglutinines were still detectable.

5. Transfusion therapy profile – We calculated the volume of erythrocytes and the number of platelet units transfused per patient in the post-transplantation period and compared it with that of the control group.

Table 2 – HES Sedimentation (12 B.M.)

Erythrocyte contamination
residual volume (ml): 27,4±13,5
removal (%): 92,4±3,6
infused erythrocytes (ml/kg): 0,18

Recovery of nucleated cells (%)
76,2±9,8

Number of cells injected (cells/Kg)
2,16±0,48

average values ± standard deviation

RESULTS

1. Erythrocyte depletion – Twelve bone marrows were gravity sedimented by HES. The average erythrocyte removal was 92,4% ± 3,6, corresponding to an infusion of 0,55ml ± 0,18 of erythrocytes per Kg of weight. The average number of cells collected was 2,9 x 10^8 per Kg, with a recovery of 76,2% ± 9,8 after sedimentation, corresponding to 2,16 ± 0,48 injected cells per Kg *(Table 3)*.

2. Acute Hemolysis – One episode of acute hemolysis occurred in patient UPN 43 during cell reinforcement on day + 27. A total of 51.3 ml of erythrocytes (0.9 ml of erythrocytes per Kg of weight) were infused, the patient presenting anti-A agglutinines with a titer of 8 on this date.

Table 3 – Hematopoiesis onset (peripheral blood)

	Recovery time (days)		
	study g.	**control g.**	**p.**
Neutrophils ≥500/ul	24,4±11,7	20,9±6,2	0,096 (n.s.)
Platelets ≥25,000/ul	31,7±22,0	23,8±16,6	0,099 (n.s.)
Reticulocytes > 1%	66,3±109,0	24,7±10,8	0,018 (s.)

Average values ± standard deviation
p <0,05

3. Delayed hemolysis – Patient UPN 25 registered a sharp reduction of hemoglobin - 4g/dl less on day +87 - for a period of about 40 days, corresponding to an episode of retarded hemolysis with laboratory evidence.

4. Hematopoiesis onset – In what concerns the beginning of myelopoiesis and of megakario poiesis there were no significant differences observed between the groups studied, contrary to erythropoiesis which began on day +66 - average value - in the study group and +25 in the control group *(Table 3)*.

5. Persistence of agglutinines – In all the patients, except one, anti - A and anti - B agglutinines disappeared by day +60; patient UPN 6 still had anti - A until day +418 *(Table 4)*.

6. Transfusion therapy profile - The study group presented an average individual erythrocyte consumption of 3.046 cc ± 3,863 and an average individual platelet consumption of 55,5 u. ± 37,0, while in the control group these items were 759 cc ± 986 of erythrocytes and 38,7 u. ± 39,6 of platelets respectively. Table 5 presents the results per Kg of weight of each individual.

Table 4 – Persistence of anti - A and anti - B agglutinines

Number of days in which agglutinines were detectable: 67,2 ± 71,2		
UPN 06 - 418	UPN 25 - 47	UPN 39 - 20
UPN 12 - 30	UPN 27 - 30	UPN 41 - 30
UPN 22 - 46	UPN 31 - 30	UPN 43 - 30
UPN 23 - 30	UPN 35 - 35	UPN 45 - 60

average ± standard deviation
NB: UPN 50 was not referred as day +30 had not yet been reached

To summarise, we may say that seven patients presented some type of immuno-hematological consequences of their ABO incompatibility with the donor, although only one with long term biological repercussions (Table 6).

DISCUSSION

Major ABO incompatibility occurs in 10 to 12% of identical HLA B.M. transplants [1]. The first successful ABO incompatible transplants. were described in 1977/1978 [2,3], and a greater incidence of graft rejection or of G.V.H.D. [4,5] was not verified in these patients despite the specific differences between the ABO groups [6]. It is possible to minimize the immuno-hematological problems of this particular type of B.M.T. by reducing the titer of ABO antibodies circulating in the receiver or diminishing the volume of erythrocytes in the donor B.M. [7-12].

In this study we assessed 13 patients submitted to identical A and B HLA B.M.T. with negative M.L.C. and major incompatibility in the ABO system (sometimes associated to minor).

The analysis of the results obtained with the HES sedimentation technique shows that they are similar to numbers mentioned in the literature in what concerns recovery of nucleated cells but worse as regards erythrocyte contamination [11,13].

Table 5 – Transfusion therapy

	study g.	control g	p.
Erythrocytes (cc/kg weight)	58,49±63,60	1,99±2,54	0,0001 (s.)
Platelets (u/kg weight)	1,10±0,80	0,87±0,90	0,218 (n.s.)

Average values ± standard deviation
p <0,05

Table 6 – Immuno-Hematological Consequences (7 patients)

UPN 06	– Delayed erythropoiesis onset (D+424), agglutinine persistence (more than 120 days) and increase of support in erythrocytes
UPN 22	– Erythrocytes (49 units)
UPN 25	– Increased erythrocyte support (17 units) retarded hemolysis
UPN 31	– Increased erythrocyte support (14 units)
UPN 41	– Delayed erythropoiesis onset (D+79)
UPN 45	– Increased erythrocyte support (15 units)

The only case of delayed hemolysis occurred within the time described in the literature [14] and was due to a high number of contaminating erythrocytes. The persistence (or return) of ABO agglutinines may provoke delayed hemolysis and postpone erythropoiesis onset, when the titer is 16 or above [9],or even lead to graft failure [15]. In this study, only patient whose ABO antibodies persisted for more than 120 days was a patient with severe Aplastic Anemia conditioned with CPP alone.

Although some groups state that major ABO incompatibility may affect the three cell lineages [15,16] it seems more probable that it only delays erythropoiesis onset [9,10,14] due to the fact that eritroid lineage precursors express ABH antigens [16] (some authors disagree [17]). Our results confirm this conclusion since we verified a significant difference between both groups.

To conclude, we would like to emphasize how relevant erythrocyte consumption was in the incompatible ABO group, in which the average value for these patients surpassed those of the control group in more than 2 litres, in total agreement with results in literature [5,18,19].

ACKNOWLEDGEMENTS

We wish to thank Dr. Nuno Miranda, who was responsible for the statistical analysis, for his technical collaboration.

REFERENCES

1. BENSINGER WI, BUCKNER CD, THOMAS ED, CLIFT RA: ABO incompatible marrow transplants. Transplantation 1982; 33: 427-429.

2. GALE RP, FEIG S, HO W et al: ABO blood group system and BMT. Blood 1977; 50: 185-188.
3. BUCKNER CA, CLIFT RA, SAUNDERS JE et al: ABO-incompatible marrow transplants. Transplantation 1978; 26: 233-237
4. HERSCHKO C, GALE RP, HO W, FITCHEN J: ABH antigens and BMT. Br J Hematology 1980; 44: 65-73.
5. KOCH PA, BARNSLEY W, SEROTA FT, BALKE MB, AUGUSTUS CS: ABO mismatched BMT in children. Exp Hematol 1978; 7: 9-11
6. REVIRON J, SCHENMETZLER C, BUSSEL A, DEVERGIE A, GLUCKMAN E.: Evidence for different kinds of major ABO incompatibility in transplantation in the management of 62 bone marrow recipients Transplantation Proceedings 1987, XIX (6): 4623-4628.
7. LASKY LC, WARKENTIN PI, VERSEY JH, RAMSAY NKC, McGLAVE PB, McCULLOUGH J.: Hemotherapy in patients undergoing blood group incompatible BMT. Transfusion 1983; 23: 277-285.
8. BENSINGER WI, BAKEN BA, BUCKNER CD, CLIFT RA, THOMAS ED.: Immunoadsorption for removal of A and B blood group antibodies New E J Med 1981; 304: 160-162.
9. BRAINE HG, SENSENBRENNER LL, WRIGHT SK, TUTSCHKA PJ, SAVEL R, SANTOS GW.: Bone Marrow Transplantation with major ABO blood group incompatibility using erythrocyte depletion of marrow prior to infusion. Blood 1982; 60: 420-425
10. BLACKLOCK HA, PRENTICE RG, EVANS JPM, KNIGHT CBT, GILMORE MJML et al: ABO incompatible BMT: Removal of red blood cells from donnor marrow avoiding recipient antibody depletion. Lancet 1982; 2: 1061-64
11. DINSMORE RE, REICH LM, KAPOOR N, GULATI S et al: ABH incompatible BMT: removal of erythrocytes by starch sedimentation. Br J Hematol 1983; 54: 441-449
12. FALKENBURG JHF, SCHAAFSMA MR et al: Recovery of hematopoeisis after blood group incompatible BMT with red blood cell depleted grafts. Transplantation 1984; 39 (5): 514-520.
13.WARKENTIN PL, HILDEN JM, KERSEY JH, RAMSAY NKC, McCULLOUGH J: Transplantation of major ABO incompatible BM depleted of red cells by HES. Vox Sang 1985; 48: 89-104
14. SNIECINSKI IJ, OIEN L, PETZ LD, BLUME KG: Immunohematological consequences of major ABO mismatched bone marrow transplantation. Transplantation 1988; 45 (3): 530-534
15 . GROW RS, KORMEYER GDR YANKEE RA et al: ABO blood group system in Acute Leukemia employing ciclophosphamid. Exp Hematol 1972;22: 118-120
16.BLACHLOCK HA, KATZF, MICHALEVITZR et al: A and B antigen expression on mixed colony cells and erythroid precursors: relevance for human allogeneic BMT BR J Hematol 1984; 58: 267-269
17. BENSINGER W, PETERSON FB, BARAJI M, BUCKNER CD, CLIFT R, SLICHTER SJ STORB R: THomas ED. Engraftment and transfusion requirements after allogeneic marrow transplant for patients with acute non-lymphocytic leukemia in first complete remission. Bone Marrow Transplantation 1989; 4:409-414
18. JIM NR, HILL R, SEYAL S: Preparation of red blood-cell depleted marrow for ABO incompatible marrow transplantation by density-gradient separation using the IBM 2991 blood cell separator. Exp Hematol 1987; 15: 93-96
19. PETZ LD, SCOTT EPP: Supportive Care in Clinical Bone Marrow Transplantation. Editors: Blume KG, Petz LD. Churchill Livingstone, NY 1983