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, INÉS 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 ral 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 transfusion support. We concluded that major ABO incompatibility does not constitute a drawback to BMT success in most patients.

INTRODUCTION

Initially considered as a contraindication 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 erythropoiesis 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 Hydroxyethyl 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.
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 hydration 24 hours before the B.M.T.- 3.000 cc of 5% dextrose in saline solution per m² 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 HL A 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. Hematopoiesis 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.

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 10⁸ 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.

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 megakaryopoiesis 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

<table>
<thead>
<tr>
<th></th>
<th>study g.</th>
<th>control g.</th>
<th>p.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes</td>
<td>58,49±63,60</td>
<td>1,99±2,54</td>
<td>0,0001 (s.)</td>
</tr>
<tr>
<td>Platelets</td>
<td>1,10±0,80</td>
<td>0,87±0,90</td>
<td>0,218 (n.s.)</td>
</tr>
</tbody>
</table>

Average values ± standard deviation
p <0.05

Table 6 – Immuno-Hematological Consequences (7 patients)

<table>
<thead>
<tr>
<th>Number of days</th>
<th>Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPN 06</td>
<td>Delayed erythropoiesonset (D+424), agglutinine persistence (more than 120 days) and increase of support in erythrocytes</td>
</tr>
<tr>
<td>UPN 22</td>
<td>Erythrocytes (49 units)</td>
</tr>
<tr>
<td>UPN 25</td>
<td>Increased erythrocyte support (17 units)</td>
</tr>
<tr>
<td>UPN 31</td>
<td>Increased erythrocyte support (14 units)</td>
</tr>
<tr>
<td>UPN 41</td>
<td>Delayed erythropoiesonset (D+79)</td>
</tr>
<tr>
<td>UPN 45</td>
<td>Increased erythrocyte support (15 units)</td>
</tr>
</tbody>
</table>

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

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REFERENCES

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.