



# e-Network Forum

## CALIFORNIA BLOOD BANK SOCIETY

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### ***Selection of Red Cells for supporting Rh-positive recipients of Rh-negative marrow during and after engraftment***

**A transfusion medicine physician from a southern state** requests input from the e-network forum regarding a group **O Rh positive** bone marrow transplant (BMT) recipient who recently received a transplant of allogeneic marrow from a group **AB Rh negative sibling**. The BMT recipient is a teenager who is being treated for T-ALL. According to the inquiring physician the patient and sibling are both HLA identical at A2, 11, B44, 55, DR4, 15. The BMT donor has never been transfused, and is not alloimmunized to the D-antigen. At the time of this writing, the BMT recipient still types Rh positive, has a negative DAT, and currently is not showing any clinical signs of hemolysis. The BMT recipient received two units of group O Rh positive RBCs in the week **before** transplant and two units **after** the transplant. There is no evidence yet of engraftment. The inquiring physician wants to know if the BMT recipient is at risk for developing anti-D, and if so, what would members of the e-network forum do regarding transfusion of D-positive or D-negative RBCs to support transfusion requirements during and after the engraftment period.

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The following responses have been received.

- 1. A blood banking scientist in Canada** wrote that the HOST cellular immune system of the BMT recipient is not at risk of making anti-D, but the transplanted bone marrow from the Rh negative BMT donor will be exposed to the recipient Rh (D) antigen and **some engrafted lymphocytes could possibly mount an anamnestic response or a primary response and produce anti-D**. This has been documented previously for the former (Hows J et al, Blood 1984). There is not enough information given to speculate about other factors. For instance, if the BMT recipient is a male, then even if the donor BMT after engraftment produces anti-D, this may not be of much consequence. On the other hand, if anti-D is produced this could result in some significant hemolysis as pointed out in the Blood paper of Hows et al. It is possible that a delayed engraftment, if significantly delayed, may indicate a "mixed hematopoietic chimera" (Branch DR, et al, Transplantation 1982). If this is the case, the **donor BMT would likely develop tolerance to the D antigen** and anti-D production would be unlikely. To be safe, the Canadian scientist would recommend transfusing this patient with **Rh negative** RBCs.
- 2. Editor's note:** Several responding individuals **questioned** the possibility that the BMT patient could be group O and the BMT donor (a sibling) could be group AB. While the inquiring blood banker did not provide a full accounting of the ABO of the patient and sibling's parents, from a hypothetical standpoint, if a woman is genotype AO and a man is genotype BO, then one child of that mating could be group AB, another could be group O, another could be group A and yet another could be group B. Thus, as in this case, it is perfectly consistent that one sib (the BMT patient) could be group O and another sib (the BMT donor) could be group AB.
- 3. A transfusion medicine physician from New York** wrote that Rh positive individuals who receive Rh negative stem cell transplants **are at risk of Rh sensitization**. This is not too common, but does occur on occasion as the Rh antigen is not expressed except on erythroid precursors, and the donor marrow can be sensitized by recipient or transfused red cells in myeloablative transplants. The New Yorker reports that they usually would start such a patient on Rh negative red cells from the beginning of BMT planning if the recipient were a child or a woman under the age of about 40-50 years. The transfused red cells hang around a lot longer than it takes to engraft the donor immune system, so waiting to start Rh negative until the transplant is engrafted is "closing the barn door after the cow has departed". On the other hand the New Yorker would not give Rh immune globulin to prevent sensitization due to receipt of Rh positive platelet concentrates until after the recipient was clearly typing Rh negative due to the combined effects of engraftment and replacement of the donor red cells with transfused Rh negative red cells. This usually takes at least 6-8 weeks. They do not worry excessively about giving Rh positive **platelet** concentrates during the 2-4 weeks of aplasia, since recipient Rh positive red cells are usually still around for that period.
- 4. A consultant hematologist from a hospital in London, UK** wrote that **the patient is at risk of developing anti-D**. Cases of alloimmunisation to D-antigen have been reported in the setting of

a D positive recipient and a D negative donor. The London hematologist has recently seen such a case following a non-myeloablative transplant. Despite the immunosuppression the recipient is having, his residual D positive cells may present sufficient antigenic challenge. And the fact that he was transfused before and after with D positive cells doesn't help either! The hematologist's suggestion is to avoid further transfusions with D positive red cells (and perhaps even D positive platelets?).

5. **A transfusion medicine physician who is authoring a text book chapter** on Rh non-identity between allogeneic hematopoietic stem cell donor and recipient had the following to report. (The chapter from which the following was taken will be published in a Pediatric Text by Drs. Jay Herman and Catherine Manno in early 2003).

"The two possible scenarios are a Rh(D) positive donor into a Rh(D) negative recipient and a Rh(D) negative donor into a Rh(D) positive recipient. The former scenario simply means that as of infusion of the new marrow or stem cells that there is no further need to provide Rh (D) negative components, since the new immune system will tolerate Rh(D) positive red cells. While it is possible to begin administering Rh(D) positive cells at the time of admission, most transfusion services like to ensure consistency for their staff by not providing positive components until the recipient's type is officially designated as Rh(D) positive. Hence, in practice some centers will transfuse at least some Rh(D) positive components, such as platelets, from the time of admission, whereas others may wait until there is evidence of engraftment before providing Rh(D) positive red cells.

Conversely, the situation where an Rh(D) negative donor is to engraft in a formerly Rh (D) positive recipient creates the possibility that when the new immune system engrafts there could be a vigorous delayed hemolytic transfusion reaction. Depending upon the residual content of Rh(D) positive cells, up to the entire red cell mass of the patient could be subject to hemolysis. Hence, the widespread practice of providing Rh(D) negative red cell components from the time of admission, or even shortly beforehand."

6. **A transfusion medicine physician in Minnesota** reports his opinion that relative to the BMT case, the first thing to remember is that it is quite rare for recipients of allogeneic BMT to be able to mount a primary immune response to any antigen during the first year (or even longer ) after the transplant. This is particularly true if conventional chemo/radiation preparative regimens have been used. It may not be equally true after the so-called "mini-allo" transplants! By the time that the engrafting D negative marrow and immune system is capable of forming a new anti-D , the D positive original recipient red blood cells (or even transfused cells from the transplant period) will have long disappeared from the circulation. There are rare instances of patients forming new alloantibodies early in the process and the responding Minnesotan reported such a case in 1985 (Moore SB et al, A Case of Unusually Early But Temporary Immune Reconstitution After Bone Marrow Transplantation. Transplantation 1985; 39:675-677).

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7. **A transfusion medicine physician from North Carolina** who is both a transfusion service medical director and a BMT Laboratory director wrote that because the donor is AB negative and the recipient is O positive, that this would present **a major ABO mismatched BMT as well as Rh mismatched BMT**. The responding blood banker wonders if the BMT protocol used full conditioning (i.e., is not a "mini" protocol), and therefore, the patient would be receiving full GVHD prophylaxis in the form of cyclosporine (or FK506) plus methotrexate or another agents. There are some case reports of primary Rh sensitization in the setting of BMT as described in this case, so primary Rh sensitization might occur. He does not believe that the issue has been studied prospectively and does not know of any data regarding quantitation of the incidence of this occurrence. Primary sensitization has been reported at 4 months and 2 years, which would seem reasonable if one were to predict when primary sensitization would occur. Since there is exposure to recipient O positive blood from Day 0, the transfusion of Rh negative products might not be useful in minimizing sensitization. However, his facility is conservative in their approach. They would **transfuse Rh negative blood products (if available) beginning on Day 0**. The incidence of primary Rh sensitization is probably most dependent on the individual's immunosuppressive (anti-GVH) regimen post transplant, any modifications of it (sometimes methotrexate is held due to the development of mucositis, even though the protocol may call for it), amount of hemorrhage, other blood loss, hemolysis, etc. **Side note:** Major **ABO**-mismatched transplants may develop pure red cell aplasia (PRCA). This is less likely if the patient has received myeloablative conditioning and/or receives less GVHD prophylaxis.

References:

- Gandini G, et al. Detection of an anti-RhD antibody 2 years after sensitization in a patient who had undergone an allogeneic BMT. Bone Marrow Transplant. 2000 Feb;25(4)457-9.
- Heim MU, et al. Rh antibodies against the pretransplant red cells following Rh-incompatible bone marrow transplantation. Transfusion 1988 May-June;28(3)272-5.

8. **A transfusion medicine physician in Chicago** wrote that in his practice, they would switch the

patient to Rh-negative RBCs at the time of transplant, supply permitting. He believes there have been reported cases of anti-D arising later from the new Rh-negative immune system, after sensitization from the residual Rh positive RBCs still circulating, but it's not very practical to do much to prevent it, say in a girl or young woman, except for giving Rh-negative RBC transfusions as needed. The anti-graft-vs-host medications (cyclosporine, methotrexate, or other immunosuppressives) might reduce the risk of primary RBC alloimmunization following engraftment.

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**Addenda:** July 11 & 13, 2002