TRANSFUSION MEDICINE MINUTE: Serologic Interference with Anti-CD38 Therapy in Multiple Myeloma Patients

Transfusion Medicine Practitioner News <transfusionmedicine@bloodsystems.org>

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To: Oneill, Janette <Janette.Oneill@ventura.org>;

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Serologic Interference with Anti-CD38 Therapy in Multiple Myeloma Patients

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(February 19, 2016) - The physicians of Blood Centers of the Pacific and United Blood Services have reviewed the 2016 AABB Association Bulletin (#16-02) on "Mitigating the Anti-CD38 Interference with Serologic Testing" and recent publications on the effect of daratumumab (i.e. DARZALEX™ or DARA) on serologic testing. The following provides some background information and recommendations to mitigate the serologic interference which could delay appropriate patient care and transfusions.

We strongly recommend that you share this information with clinical leaders in oncology and hematology and with management for pharmacy and nursing so that the transfusion service is notified whenever a patient is scheduled to begin or has begun DARA treatment.

DARA, from Janssen Biotech (Johnson & Johnson), is a new drug recently approved by the FDA to treat patients with refractory multiple myeloma. This monoclonal antibody is directed against CD38, which is strongly expressed on malignant plasma cells, but also weakly present on red blood cells (RBCs). Therefore, DARA can bind to RBCs and interfere with antibody screening, antibody identification and compatibility testing. Patients may be on this treatment for 6 months or more, and the RBC binding effects of the drug may persist for up to 6 months after drug discontinuation. Possible side effects of the drug include anemia and thrombocytopenia, which may require chronic transfusion support.

We would like to make these important points to hospital transfusion services regarding the effects of DARA on pre-transfusion testing:

1. ABO/RhD typing is NOT impacted
2. Panreactive weak antibody is seen on antibody screen and antibody panel; stronger reactions may also be seen
3. DAT/Autocontrol may be positive or negative
4. Anti-human globulin (AHG) crossmatches will be positive with all RBC units tested
5. Adsorptions do not eliminate pan-reactivity

To prevent delays in providing blood for patients on an anti-CD38 medication, we would like to supplement points made in the AABB bulletin regarding antibody screen and antibody identification protocols:

1. The hospital transfusion service should work with pharmacy and clinical services to develop a protocol (i.e. CPOE process automation) that requires notification of the transfusion service whenever a patient is scheduled to begin DARA therapy or is known to be on this medication and may require blood.
2. If a patient's serum exhibits pan-reactivity and clinical history is not known, the clinical record should be searched or the clinical team contacted for a history of multiple myeloma and DARA treatment whenever possible.
3. BEFORE a patient begins taking anti-CD38
   - Before DARA is started, perform a baseline antibody screen and identification.
   - Perform a baseline extended phenotype or genotype to determine which clinically significant antibodies the patient could form following transfusion.
4. AFTER a patient begins taking anti-CD38
   - ABO/RhD typing can be performed normally
   - For antibody detection/identification, DTT-treated cells can eliminate the interference since DTT denatures CD38. If the hospital blood bank cannot DTT treat panel cells, send sample to an Immunohematology Reference Lab (see sample requirements section).
   - DTT treatment destroys Kell system antigens. Thus, anti-K cannot be ruled out in K-negative (K-) patients. However, anti-K may be ruled out using cord cells.
   - DTT also destroys other antigens (e.g. k, Yt^a, Do^a,Do^b, etc.), so antibodies against these antigens, although infrequent, will not be detectable with DTT-treated cells.

For crossmatching protocols for DARA patients, we also make the following recommendations:

1. If antibody screen using DTT-treated cells is negative, then perform an electronic or immediate spin crossmatch on blood that is ABO/RhD compatible AND K-negative (unless patient is K-positive [K+] or anti-K has been ruled out).
2. If allo-antibodies are detected with DTT-treated cells, then perform an AHG crossmatch on blood that is ABO/RhD compatible AND K-negative (unless patient is K+ or anti-K has been ruled out) AND negative for other antigens against which clinically-significant antibodies were identified.
3. If the patient has known allo-antibodies and known RBC phenotype/genotype, phenotypically/genotypically matched RBC units may be selected for AHG crossmatch.
4. If DTT treatment cannot be performed or results are not yet available and the patient's RBC phenotype/genotype is known, select phenotypically/genotypically matched RBC units for AHG crossmatch.
5. If an emergency transfusion is required, uncrossmatched ABO/RhD-compatible RBCs may be given per hospital policy.
6. It is important to note that all AHG crossmatches, even with phenotypically/genotypically matched RBCs, will be **incompatible**. Issued units may need to be labeled as "incompatible," and clinical teams should be notified per hospital policy.

Samples Requirements for the Immunohematology Reference Lab (IRL):

- INDICATE ON IRL ORDER FORM THAT PATIENT IS ON DARA OR SCHEDULED TO START DARA
- For new patients scheduled to begin DARA – Send 1 EDTA tube for phenotype/genotype
- For a patient on DARA and RBC phenotype/genotype is NOT known – Send 3-4 EDTA tubes for antibody screen, antibody identification, DTT treatment, and phenotype/genotype
- For a patient on DARA with known RBC phenotype/genotype – Send 2-3 EDTA tubes for antibody screen, antibody identification, and DTT treatment
- Note, we recommend establishing a **baseline molecular genotype** for all patients undergoing DARA treatment. The advantage of the molecular genotype is that it also defines genotypes for k, Kp^a, Kp^b, Js^a, Js^b, Do^a, Do^b, Hy, Jo^a and LW, which are antigens sensitive to or destroyed by DTT. A molecular genotype can be performed after DARA administration.

Citations:

1. Association Bulletin #16-02. AABB, January 15, 2016.
2. Darzalex package insert. Horsham, PA: Janssen Biotech, 2015. [Available at: http://www.darzalex.com/shared/product/darzalex/darzalex-prescribing-information.pdf (accessed January 25, 2016).]
3. Oostendorp M, Lammerts van Bueren JJ, Doshi P, Khan I, Ahmadi T, Parren PWHI, van Solinge WW, De Vooght KMK. When blood transfusion medicine becomes complicated due to interference by monoclonal antibody therapy. Transfusion. 2015;55(6 Pt 2):1555-62.
   Chapuy CI, Nicholson RT, Aguad MD, Chapuy B, Laubach JP, Richardson PG, Doshi P, Kaufman RM. Resolving the daratumumab interference with blood compatibility testing. Transfusion. 2015;55(6 Pt 2):1545-54.

If you have questions about IRL testing for patients on or starting daratumumab, please contact any of our physicians directly. To discuss a transfusion-related issue with an on-call physician, please call our Transfusion Medicine Hotline at 1 (800) 811-2581.