Advancing Transfusion and Cellular Therapies Worldwide

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To: AABB Members

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Re: Mitigating the Anti-CD38 Interference with Serologic Testing

Summary
A class of therapeutic agents originally approved for multiple myeloma, monoclonal antibodies to CD38, can result in interference with blood bank serologic tests and thereby cause delays in issuing Red Blood Cell (RBC) units to patients receiving these agents. To minimize these delays, hospitals should set up procedures to inform the transfusion service when patients start receiving these agents. Considerations for the transfusion service, both before and after initiation of anti-CD38 therapy, are detailed below.

The AABB Clinical Transfusion Medicine Committee and Transfusion Medicine Subsection Coordinating Committee has developed this bulletin to provide background information and guidance to members regarding anti-CD38 interference with serologic testing.

Association Bulletins, which are approved for distribution by the AABB Board of Directors, may include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin contains information and recommendations. No new standards are proposed.

Background
Anti-CD38 monoclonal antibodies are a treatment for multiple myeloma
CD38 is an integral membrane protein that is highly expressed on myeloma cells that has been shown to be an effective target antigen for monoclonal antibody therapies. There are currently two anti-CD38 monoclonal antibodies approved by the Food and Drug Administration, daratumumab **(Darzalex)** and isatuximab **(Sarclisa)**. **Daratumumab is also available as a subcutaneous formulation combined with hyaluronidase (Darzalex Faspro)**[1]. However, there are other anti-CD38 monoclonal antibodies under development and in trials. In addition, new off label uses for anti-CD38 monoclonal antibodies are coming into clinical practice.

Of note, anti-CD38 may cause a small decrease in hemoglobin in vivo (~1 g/dL), but severe hemolysis has not been observed among treated patients.[2, 3, ~~6~~]

Anti-CD38 monoclonal antibodies interfere with blood bank serologic tests
In addition to immune cells, CD38 is weakly expressed on red cells. Anti-CD38 binds to CD38 on reagent RBCs, causing panreactivity in vitro.[2,3,4] Plasma samples from anti-CD38-treated patients consistently cause positive reactions in indirect antiglobulin tests (IATs), antibody detection (screening) tests, antibody identification panels, and anti-human globulin (AHG) crossmatches. Agglutination due to anti-CD38 may occur in all media (eg, saline, low ionic strength saline, polyethylene glycol), and with all IAT methods (eg, gel, tube, solid phase). Agglutination reactions caused by anti-CD38 are usually weak (1+), but stronger reactions (up to 4+) may be seen in solid-phase testing. However, anti-CD38 does NOT interfere with ABO/RhD typing or with immediate-spin crossmatches.

Other notes on anti-CD38 serologic interference:

- Dithiothreitol (DTT)-treated cells eliminate the interference.[4,5,2,7]
- Cord blood cells lack CD38 antigen and could be used to eliminate interference if available and especially considered in patients with anti-K or other suspected antibody to antigen denatured by DTT-treatment.[6,9]
- Adsorptions using either untreated or ZZAP-treated cells fail to eliminate the interference.
- Anti-CD38 may result in a positive IgG direct antiglobulin test (DAT) and autocontrols tested in antibody identification panel.
- Some rare dominant Lu(a–b–) cells are not reactive in the presence of anti-CD38, potentially giving the false impression that the patient has a Lutheran-related antibody.[7,8,4,5]
- Positive IATs can be observed for up to six months after anti-CD38 is discontinued.[2, 9,1,3]

Anti-CD38 interference can cause delays in issuing RBCs
If the transfusion service is unaware that a patient has received anti-CD38, the following scenario may occur when the patient's sample is tested:

Test	Negative (no interference)	Positive (reactive with all cells)	Negative or positive
ABO/RhD typing	X	N/A	N/A
Antibody detection ("screen")	N/A	X	N/A
Antibody identification	N/A	X	N/A
DAT	N/A		X

IS crossmatch	N/A	X	N/A
AHG crossmatch*	N/A	X	N/A

*AHG crossmatch compatible with DTT-treated cells

This leads to delays in issuing RBCs to the patient. In some cases, the anti-CD38 interference could mask the presence of a clinically significant alloantibody.

Recommendations
To avoid problems with transfusion, hospitals should set up procedures to inform the transfusion service whenever any patient is scheduled to begin taking anti-CD38.

BEFORE a patient begins taking anti-CD38:

- A baseline type and screen should be performed.
- In addition, a baseline phenotype or genotype may be considered. Genotyping can be performed after the patient receives anti-CD38.
    - Given **the very** low rate of alloimmunization **(0.4 – 4.1%)** in cohorts of multiple myeloma patients receiving anti-CD38 therapeutic monoclonal antibodies, **multiple large studies now support** ~~some studies suggest~~ a more targeted approach for extended antigen phenotyping/genotyping.[10,11,12] **Some institutions use only ABO/RhD and K antigen matching without extended phenotyping.**

AFTER a patient begins taking anti-CD38:

- ABO/RhD typing can be performed normally.
- For antibody detection (screening) and identification, dithiothreitol (DTT)-treated cells can be used to eliminate the interference.[4, 5~~2,7~~]
    - Because DTT treatment destroys Kell antigens**,** K-negative units should be provided unless the patient is known to be K-positive.
    - Antibodies against other DTT-sensitive blood group antigens (anti-k, anti-Yt^a, anti-Do^a/Do^b, etc) will not be detectable when the antibody screen with DTT-treated cells is performed; such antibodies are encountered infrequently, however.

Crossmatch

- For patients with a negative antibody screen using DTT-treated cells, an electronic or immediate-spin crossmatch with ABO/RhD-compatible, K-matched units may be performed.
- For patients with known alloantibodies, phenotypically or genotypically matched RBC units may be provided.[3, 13~~6,8~~]
    - As some typing antisera require the use of AHG, phenotyping should be performed before the patient receives anti-CD38.
    - AHG crossmatches with phenotypically or genotypically matched units will still be incompatible.
- Alternatively, an AHG crossmatch may be performed using DTT-treated donor cells (K-matched units).

Other notes on issuing blood for transfusion

- Some clinically significant antibodies may be missed with the use of uncrossmatched phenotypically or genotypically matched units, although this will occur infrequently **due to the immunosuppressive effects of anti-CD38 antibodies and/or the underlying disease**.
- If an emergency transfusion is required, uncrossmatched ABO/RhD-compatible RBCs may be given per local blood bank practices.
- **Effective communication between clinical services and transfusion services may be beneficial for optimal management of patients receiving anti-CD38 therapy.**

Future/alternative approaches to mitigating the anti-CD38 interference

Several alternative methods to mitigate anti-CD38 interference are commercially available:

- **Anti-idiotype antibodies: Recombinant monoclonal anti-daratumumab antibodies that neutralize daratumumab in patient plasma are now commercially available with a 93% success rate. These reagents are specific to daratumumab; different idiotype antibodies would be needed for other anti-CD38 therapeutics.[14]**

- **Soluble CD38 reagents: Multiple commercially available soluble CD38 products neutralize anti-CD38 in patient plasma, eliminating interference with reagent or donor red blood cells.**

- **Fab fragment reagents: Fab fragments that mask CD38 antigens to prevent anti-CD38 binding to red blood cells without destroying Kell antigens have been validated.[15]**

- **Trypsin-based methods: Trypsin treatment of reagent cells has demonstrated 98.4% success rate in eliminating daratumumab interference.[16]**

- **Lower DTT concentrations: Some laboratories have reported using 0.01M or 0.04M DTT (rather than 0.2M) to remove daratumumab interference while preserving Kell blood group antigenicity, though additional validation is needed before widespread implementation.[17, 18]**

- **Antigen-typed cord cells, which lack CD38 antigen, can be used for the antibody screening as an alternative to DTT-treated cells. [6]**

~~It is possible to neutralize anti-CD38 in plasma and eliminate the interference using either recombinant soluble human CD38 or daratumumab idiotype antibody.[2,3] Neither reagent is widely available at this time, and additional validation would be needed. In principle, soluble CD38 could be used to neutralize any anti-CD38, while different idiotype antibodies would be needed to neutralize different CD38 therapeutic antibodies. Antigen-typed cord cells have been used for the antibody screen as an alternative to DTT-treated cells.[9]~~ There is a report that a manual polybrene method with standard PEG-IAT can also eliminate daratumumab interference, but may still not provide adequate sensitivity in the Kell system.[13]**[19]** ~~Some groups have reported using 0.01M or 0.04M rather than 0.2M DTT-treated reagent red cells to remove daratumuamb interference while preserving Kell blood group antigenicity.[14,15] Additional validation of these lower DTT concentrations would be needed.~~

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