

PEARLS OF LABORATORY MEDICINE

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TITLE: Daratumumab Interference in Pre-Transfusion Testing

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Hello, my name is Aleh Bobr. I am an assistant professor and medical director of blood bank and tissue services at University of Nebraska Medical Center in Omaha, NE. Welcome to this Pearl of Laboratory Medicine on “**Daratumumab Interference in Pre-Transfusion Testing.**”

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Multiple myeloma (MM) is a hematologic malignancy affecting antibody producing plasma cells.

One of the targeted antibody based therapies is Daratumumab (DARA), a human IgG1K monoclonal antibody that targets the CD38 glycoprotein located on the cellular surface of the neoplastic plasma cells.

It is currently approved by FDA for MM patients who have received only one prior therapy. This approval by the FDA came as the result of two simultaneous clinical trials demonstrating similar and “substantial improvements” in progression free survival despite different accompanying drug regimens, proving that DARA was the primary agent responsible for the improved clinical endpoints.

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CD38, besides being expressed on plasma cells, is also expressed on multiple other hematologic cell types including red blood cells (RBCs), medullary thymocytes, activated B and T cells, natural killer cells, monocytes, granulocytes, and others.

This expression led to interference of Daratumumab in the assays that use secondary anti-human IgG antibody for amplification of signal, such as AHG phase of red cell antibody screen and others

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Let's discuss a typical case of Daratumumab interference

60 year old female patient, undergoing treatment for multiple myeloma was found to have low hemoglobin and needed transfusion. A routine red cell antibody screen test was submitted to hospital's transfusion medicine laboratory and results are shown below.

The image below shows typical pre transfusion antibody screen. The purpose of the test is to identify any antibodies that present in recipient serum and that may cause hemolysis of transfused RBCs. 3 different screening cells with different antigen phenotype is used for screening. The testing uses anti human globulin (AHG) as enhancer of the reaction to detect binding of antibodies to the screening cells.

In this case all screening cells show weakly positive reaction, while autocontrol – recipient own cells – is negative. Since selection of antigen combination in 3 cell panel is limited, the next step is to perform extended panel, testing larger number of screening cells to identify antibody present in recipient serum

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The image here is representative of extended RBC antibody screen with multiple different cells tested. All of the cells, excluding autocontrol show positive reaction at AHG phase of the test. This pattern is considered pan-reactive

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Pan-reactivity in antibody screen has the following differential diagnosis. If autocontrol is positive alongside all other tested cells, then we are dealing with either cold or warm

autoantibodies. If autocontrol is negative, this pattern is usually found in the situation of antibody toward high incidence antigen. Additionally, interference from monoclonal antibodies, like Daratumumab can present with pan reactivity pattern either with or without positive auto control. The more common situation in Daratumumab cases is negative autocontrol.

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Logically thinking, non specific binding of Daratumumab to RBC should have mimicked the autoantibody pattern. That is why presence of negative autocontrol in majority of Daratumumab patients created confusion among blood bankers. Recently, studies on immunomodulation helped explain this phenomenon.

Immunomodulation is selective removal of antigen from RBC membrane by spleen monocytes, when they are passing through spleen.

It was shown in the models explaining RhIG and anti Kell immunoglobulin prophylaxis. In these models, the transfused cells in the presence of antibody were either removed or lost antigen from their membrane, which mimics Daratumumab situation.

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In our case Negative autocontrol effectively rules out warm and cold autoantibodies. The differentiation between antibody toward high incidence antigen and Daratumumab or other monoclonal therapeutic antibody interference require review of medication administration records and/or special technics in transfusion laboratory

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The most commonly accepted technique in transfusion labs that helps distinguish and overcome Daratumumab interference is pre treatment of screening cells with DTT. DTT destroys CD38 on the surface of red cells and as such Daratumumab will not bind screening cells. In terms of test interpretation it will look like pan-reactivity disappears after DTT pre treatment. At the same time DTT also destroys antigens from Kell blood group and makes impossible testing for the presence of anti Kell antibodies. In other

words we can not tell for sure whether the pan reactivity is due to Daratumumab or high incidence antigen from Kell blood group.

DTT may destroy antigens from other blood groups as well (like LW), but they are either rare or clinically insignificant.

Other techniques, like using enzymes, (papain) can be useful in distinguishing high incidence antigens

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Here is an example of antibody screen performed with DTT treated screening cells. As you can see, there is no reaction between patient serum and screening cells and the screen is negative.

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The big limitation of this method is inability to rule out Kell blood group antibodies. That is why 2 practical approaches had been developed. If blood bank is notified prior to Daratumumab treatment, then the patient can be tested for Kell antigen and Kell matched blood can be provided afterward. If this notification did not happen, the only option that remains is to use DTT treatment to exclude antibodies from all groups but Kell and provide Kell negative blood to this recipient. From clinical experience, the patients with treated with Daratumumab are very unlikely to make additional antibodies and, as such, releasing K negative units is safe practice despite incompatible crossmatches in these patients.

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Antibody screen is not the only assay affected by Daratumumab. All assays that use secondary antihuman antibodies and test the cells that have CD38 expression can be affected. The following assays were reported to be affected by Daratumumab in literature:

Red cell antibody screening

Anti Neutrophil Antibody testing

Anti platelet antibody testing

Platelet crossmatch

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DTT is not the only strategy used to overcome interference, but it is cheap and widely accepted. The other approaches that have been tried include:

soluble CD38 antigen

anti-idiotypic antibody

F(ab')₂ fragments of DARA

blocking mouse anti CD38 antibody

Cord blood testing

But all of them are more expensive than DTT or not commercially available.

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Now at the end of the case let's summarize the conclusions:

Daratumumab is a humanized antibody for treatment of multiple Myeloma that can cause interference due to not specific binding.

The most affected assay is red cell antibody screen, but other assays that use secondary anti human antibody can be affected as well.

The accepted approach to overcome interference is pre-treatment of the cells with DTT that destroys CD38. Other approaches have been tried, but not currently commercially available or accepted

Slide 15: References

Thank you for your attention and for the opportunity to share the knowledge!

Slide 16: Disclosures

Slide 17: Thank You from www.TraineeCouncil.org

Pearls of Laboratory Medicine

Title

Thank you for joining me on this Pearl of Laboratory Medicine on “**Daratumumab Interference in Pre-Transfusion Testing.**”

