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Daratumumab and Multiple Myeloma
Challenges and Complications in the Blood Bank

Multiple Myeloma (MM), a cancer of malignant plasma cells in bone marrow, affected over 95,000 Americans with approximately 26,000 new cases diagnosed and over 11,000 deaths in 2015. Higher risk groups include individuals over 65 years of age, males and African-Americans, who are twice as likely to develop MM as Caucasian Americans.[1]

Daratumumab and Serological Testing Interference

In November of 2015, the FDA granted accelerated approval for daratumumab (DARA), a monoclonal antibody approved for the treatment of MM in patients who have received at least three prior treatments. DARA specifically targets human CD38, which is strongly expressed on MM cells and was shown to effectively kill these cells in clinical trials.[2] In addition to strong expression on MM cells, CD38 is also weakly expressed on normal red blood cells (RBCs), which has been reported to cause interference with immunohematology serological testing for antibody detection and identification.[3,4,5]

The DARA anti-CD38 in the patient's plasma binds to the CD38 expressed on the reagent RBCs used in antibody detection, causing a weak false positive result in the indirect antiglobulin test (IAT) and may mask underlying clinically significant antibodies in the patient's plasma. This interference may be seen in the IAT for up to 6 months after the last DARA infusion. Red cell transfusions and the transfusion services department play a critical role in the care of MM patients as anemia has been reported in one third of MM patients being treated with DARA and two thirds of all MM patients.[7] It is critical for transfusion services staff to eliminate this interference while maintaining the ability to detect clinically significant alloantibodies in pre-transfusion screening.

Dithiothreitol (DTT) Treatment

It has been reported previously that CD38 is sensitive to treatment with dithiothreitol (DTT), a reducing agent that disrupts the disulfide bonds present in human CD38.[4,5] When reagent RBCs are treated with DTT, the disulfide bonds are reduced and the shape of the CD38 protein is changed, preventing the binding with DARA. DTT treatment will typically remove all anti-CD38 activity from the antibody screen and identification test, allowing for transfusion services technologists to detect and identify any remaining clinically significant antibodies, if present, in the patient's plasma.

DTT, which is available in powder form, must be diluted to an appropriate concentration (0.2M) suitable for RBC treatment.[7] This process requires precise measurement of the DTT powder and diluent to ensure a proper final concentration, as well as extreme caution when handling DTT powder due to its hazardous nature as an irritant to the skin and mucus membranes.

DTT in the Transfusion Service

OhioHealth Riverside Methodist Hospital is a large tertiary care facility that has recently implemented a testing protocol using DTT-treated reagent RBCs. Due to significant cost and time savings over referring this testing to an immunohematology reference laboratory (IRL), the practice at Riverside is to perform this testing in house using commercially prepared 0.2M DTT. According to Nancy Fulton, MT(ASCP), central laboratory manager for transfusion service and safety at OhioHealth Laboratory Services, a type and screen (T&S) and antigen phenotype are performed before DARA treatment. A T&S will be performed on subsequent samples and, if positive, an antibody identification panel and DTT treated antibody screen using PeG enhancement will be performed. According to Fulton, her staff has seen variable anti-CD38 reactivity in the IAT, up to 1+ in strength.

There are limitations to the use of DTT treated cells in testing, as there are other blood group antigens that are sensitive to DTT treatment-most notably the Kell blood group. As a result, if testing is negative using the DTT treated screen, antibodies to Kell group antigens cannot be excluded so K negative units of blood are selected and cross-matched electronically for transfusion. If the patient has an underlying alloantibody, donor cells are treated with DTT and cross-matched using PeG enhancement. Since this protocol was implemented in May of 2016, Riverside has had ten patients that are being managed using DTT treated cells.

DARA treatment of MM patients can cause weakly reacting false positive results in the IAT, which can delay the availability of blood for transfusion as transfusion service staff resolves the testing. Education and communication are paramount to minimizing this delay. Education of transfusion service staff and clinicians regarding the testing protocols for DARA patients and the time required to complete the testing can result in better communication regarding these patients. Communication between clinicians and transfusion service staff as to which patients are receiving DARA treatment can result in faster turnaround times for pre-transfusion testing and availability of blood for transfusion.

References:

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