The Challenges of Daratumumab in Transfusion Medicine

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ABSTRACT

The field of transfusion medicine has evolved rapidly in recent years, but the central principle of transfusion is still simple, namely, the antigen-antibody interaction. Daratumumab (DARA), a monoclonal antibody (MoAb), was developed to treat relapsed/refractory multiple myeloma (RRMM). DARA works by targeting the CD38 portion of malignant cells; however, this drug attaches to the red blood cell (RBC) reagents used in blood banks, further complicating the antibody identification work-up. The AABB (formerly known as the American Association of Blood Banks) has issued a memorandum on how blood banks can effectively address panreactivity caused by DARA. Dithiothreitol (DTT), a common reagent in blood banks, has emerged as an inexpensive and practical way to dissolve panreactivity caused by DARA. However, DTT is known to destroy the Kell antigen blood group and other, less frequently encountered blood group antigens. Other promising alternative solutions, such as umbilical cord RBCs, screening cells, and neutralization, are not widely available yet. The exploration of these issues and options, in this review of the literature, is intended to guide blood bank technologists in dealing with panagglutination reactivity caused by DARA.

Keywords: daratumumab, panreactivity, monoclonal antibody, relapsed/refractory multiple myeloma, DTT, CD38, transfusion service

Multiple myeloma (MM) is a bone marrow disorder that involves the proliferation of malignant plasma cells, causing immune suppression. Currently, MM is incurable; however, healthcare professionals are continuing to develop a wide range of therapy that aims to improve patient quality of life. Autologous stem cell transplantation (ASCT), in conjunction with high-dose therapeutic drugs such as thalidomide, bortezomib, and lenalidomide, has proven to be effective for patients with newly diagnosed MM. However, the condition of patients with relapsed/refractory multiple myeloma (RRMM) often does not respond well with ASCT and high-dose therapeutic drugs. MM can be classified as RRMM when there is a recurrence of the disease after previous response. RRMM has been defined by the following criteria: ≥25% increase in the serum or urine monoclonal protein (myeloma protein [M protein]) level or ≥25% difference between involved and uninvolved serum free light chains from its nadir, respectively, or the development of new plasmacytomas or hypocalcemia.1 Deacytelase inhibitors, monoclonal antibodies (MoAbs), and new proteasome inhibitors are emerging therapies for RRMM.2

After years of clinical trials, the United States Food and Drug Administration (FDA) finally approved daratumumab in November 2015.3 DARA is the first MoAb to be used for patients with RRMM who have received 3 previous treatments for MM and have had doubly refractory reactions to protease inhibitors and immunomodulatory agents.4 MoAbs are currently the most investigated therapeutic compounds in oncology and are a prominent new class of agents with unique mechanisms of action in the treatment of MM.5

Panreactivity, which can last 5 to 6 months,5 is a huge concern in the transfusion medicine community regarding patients with RRMM who are receiving DARA treatment and blood transfusions. The AABB (formerly known as the American Association of Blood Banks) recently issued a

Abbreviations

MM, multiple myeloma; ASCT, autologous stem cell transplantation; RRMM, relapsed/refractory multiple myeloma; MoAbs, monoclonal antibodies; FDA, United States Food and Drug Administration; CD, cluster of differentiation; RBC, red blood cell; Ig, immunoglobulin; IATs, indirect antiglobulin tests; AHG, anti-human globulin; DTT, dithiothreitol; LISs, laboratory information systems

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bulletin regarding this concern. The AABB suggested that the "hospital should set up procedures to inform the transfusion service when patients start receiving [DARA]." This suggestion was echoed in the Full Prescribing Information for Darzalex (Janssen Biotech, Inc), the brand name version of DARA, as published by the FDA. Baseline typing and screening is recommended, including baseline antigen phenotyping, or genotyping.

Cluster of differentiation (CD)38 is a protein found on the cellular surface of hematopoietic cells and immune system cells; it is strongly expressed on myeloma cells but it is weakly expressed on normal red blood cell (RBC) membranes. The results of a Western blot analysis for CD38 performed by Albeniz and coworkers showed increased CD38 expression on the RBC membranes of patients with cancer and weak expression on normal RBCs. DARA attacks CD38 + MM cells by 4 mechanisms, namely, cellular destruction in the marrow via antibody mediation, cellular destruction in the marrow via complement mediation, cross-linking with anti-human immunoglobulin (Ig)G antibody and Fc receptors on effector cells, and phagocytosis of cells.

DARA has the capability to mask clinically significant antibodies. Because antibody screen and panel reagents have RBC assay capability, one would expect panreactivity in vitro when testing patients with RRMM who are receiving DARA therapy. These reactions are typically weak (1+) but tend to get stronger with more sensitive methodologies (eg, solid phase). Further, these reactions are consistently reactive in any media (saline, low ionic strength saline, and polyethylene glycol) in indirect antiglobulin tests (IATs), antibody detection (screening) tests, antibody identification panels, and anti-human globulin (AHG) crossmatch. Patients treated with DARA typically do not exhibit problems with immediate spin crossmatches and blood typing.

Recently, Chapuy and colleagues described 5 patients receiving DARA as part of an MM clinical trial at their institution. Antibody screening test results for these patients were observed to be positive; these results interfered with blood bank testing. The researchers discovered that dithiothreitol (DTT) treatment of RBC screening cells negated the interference by DARA. DTT, which is a reducing agent, acts to denature CD38 by cleaving the disulfide bonds; however, caution is necessary because some RBC antigens, such as the Kell antigen, can be destroyed by DTT. This problem can be solved by giving packed RBCs, which react negatively to the Kell antigen, to the patient being treated with DARA. A strong alternative in denaturing CD38 is 1% trypsin because it does not destroy the Kell antigen. Schmidt et al introduced the use of umbilical cord blood reagent RBCs. Because cord blood cells contain minimal CD38, it can be assumed that those cells will be less reactive with the plasma of patients treated with DARA.

The complexity of transfusion medicine created ongoing dilemmas in patient care even before the time of pioneering biologist/physician Karl Landsteiner. New treatments emerge daily, but their adverse effects often are not recognized until clinical trials are performed. As these adverse effects are identified, resolutions are formulated and applied in research, the results of which could eventually formulate standards of practice. Currently, more antibody-based oncology medications are being evaluated and are in different steps of clinical trials. These medications, like DARA, have the capability to change the way oncology patients are treated. However, these new treatments also have the potential to interfere with testing in blood banks. Delayed transfusion due to complications caused by DARA can pose a serious threat to patient safety. This threat can be avoided easily by giving the transfusion service appropriate diagnoses, transfusion histories, and medication histories. Also, the information in this literature review will hopefully aid blood bank technologists in dealing with panreactivity caused by DARA.

Discussion

Like any other medication, DARA has advantages and disadvantages. DARA specifically targets the CD38 content of malignant cells. However, DARA can interfere in some transfusion medicine testing procedures, causing unnecessary delays in patient transfusions. To prevent delayed transfusions, the AABB suggested that RBC phenotyping and genotyping, blood typing, and antibody screening (along with antibody identification, if needed) should be performed before the initiation of DARA treatment. After DARA treatment is started, the AABB recommends that blood typing be performed, that DTT-treated cells be used for antibody screening and antibody identification, that Kell antigen negative blood be given if the Kell antigen status of the patient is unknown, that electronic and immediate spin crossmatching be performed if the patient has no underlying antibodies, and that phenotype- or genotype-matched blood be given. As mentioned previously herein, rarely clinically significant antibodies may be
missed when using DTT-treated cells; this is also true for genotypic- and phenotypic-matched blood. In emergency cases, transfusion service personnel must follow the standard practices of their facility.

The results of elution studies performed by Chapuy and colleagues confirmed the hypothesis that DARA binds to the CD38 of RBCs, causing panagglutination in antibody screens, antibody panels, and IAT crossmatches. Perhaps based on those findings, De Vooght and colleagues suggested that when patients change healthcare providers or medical facilities, or when they simply need an emergency transfusion while traveling, they should present a wallet card containing their transfusion history. Chapuy and colleagues also performed studies that focused on the interaction of DARA with reagent RBCs by experimenting with various methods, such as fluorescent-tagged anti-CD38 (flow cytometry), normal plasma spiked with various concentrations of DARA and then incubated with reagent RBCs, elution of the RBCs of patients treated with DARA, and anti-DARA used to neutralize specimens from patients treated with DARA.

ZZAP reagent contains DTT and proteolytic enzyme; it acts to denature antigens that are sensitive to both substances. ZZAP to break panreactivity was attributed to low expression of CD38 on RBCs, as supported by flow cytometric findings. In contrast, detectable removal of DARA from spiked plasma was demonstrated only after increasing the amount of transduced CD38+ human promyelocytic leukemia cells (HL60) that was used for adsorption. The researchers expected that finding because RBCs contain less surface CD38 than the transduced CD38+ HL60 cells. The elution performed on the cells of patients treated with DARA did not yield CD38-binding activity.

Neutralization was accomplished by using soluble CD38 or an anti-DARA idotype; both attach to free DARA in plasma. Neutralization, although effective and simple, is expensive and not as commercially available as DTT.

An important disadvantage for DTT is the destruction of RBC antigens, such as Cartwright (Yt), John Milton Hagen (JMH), Knops (Kn, McC, and Yk), Landsteiner-Wiener (LW), with all Kell, Lutheran, Dombrock, and Cromer blood group antigens being equally susceptible to DTT treatment. Blood bank technologists must note that other clinically significant antibodies (eg, anti-k and anti-Yta), although rare, may be missed when using DTT.

Conclusion

The advent of DARA in modern medicine has provided efficient therapy for patients with RRMM; however, it also has created complexities in testing for transfusion services. Appropriate guidance from the AABB and the drug manufacturer, supplemented with proper communication between healthcare professionals and the Transfusion Medicine department, will ensure minimal adverse impact when dealing with DARA. Reviewing patient diagnosis, patient history, and patient medications is a worthwhile laboratory practice that blood bank personnel must maintain because these actions can save huge amounts of time and resources. Many modern laboratory information systems (LISs) have the ability to create pop-up screens or warning screens that contain pertinent patient information or transfusion requirements. The transfusion service should be able to manipulate its LIS to create this screen as an additional way to catch potential errors. A national registry for patients with unusual antibodies—a system already in place in the Netherlands—can be adapted in the United States and other countries. Still, the challenges in transfusion service will continue as researchers continue to develop more MoAbs.

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