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The importance of removing interference caused by Darzalex® (daratumumab) in pre-transfusion testing

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ABSTRACT

Introduction: Multiple myeloma (MM) is a hematologic malignacy characterized by the uncontrolled proliferation of abnormal plasma cells in the bone marrow. Darzalex® (daratumumab) has emerged as a highly effective therapeutic agent for MM, offering an additional treatment option for patients who have developed resistance to other therapies. However, the use of Darzalex® poses challenges in pre-transfusion testing due to its strong binding affinity of the monoclonal anti-CD38 antibody to CD38 protein, resulting in panreactivity with test erythrocytes and complicating the detection of erythrocyte alloantibodies. The objective of this case report is to outline the procedures, significance, and methodologies for mitigating this interference using the DaraEx® reagent.

Case Report: We present the cases of three patients diagnosed with MM and treated with Darzalex® at our institution in 2023. Following the administration of Darzalex®, all three patients exhibited positive results on indirect antiglobulin tests (IAT). Cross-matching tests conducted with red blood cell concentrates also yielded positive results, with strengths ranging from 2+ to 3+. To eliminate interference, we used a specific DaraEx® reagent that utilizes Fab fragments of anti-CD38 to mitigate interference by masking CD38 on the cell surface. Subsequent application of this reagent resulted in negative IAT results for all three patients. However, one patient still displayed a weakly positive cross-matching test (<1+), suggesting that complete elimination of interference may not always be achievable with the DaraEx® method.

Conclusion: Despite the availability of reliable methods such as dithiothreitol and the DaraEx® reagent for mitigating interference, complete success in eliminating interference remains elusive. This underscores the importance of implementing proactive measures to prevent interference. Patients undergoing Darzalex® therapy should undergo comprehensive immunohematological testing before medication administration. Given the increased need for blood transfusions in MM patients, ensuring the compatibility of blood products is essential for safe transfusion practices.

Keywords: Multiple myeloma; darzalex; pre-transfusion testing; anti- CD38; DaraEx

INTRODUCTION

Multiple myeloma (MM) is a hematologic malignacy characterized by the uncontrolled proliferation of abnormal plasma cells in the bone marrow (1). Darzalex® (daratumumab) has emerged as a highly effective therapeutic agent for MM, offering an additional treatment option for patients who have developed resistance to other therapies (2). It represents the first monoclonal antibody approved for the treatment of MM following extensive clinical evaluation, receiving regulatory approval from the U.S. Food and drug administration in 2015 (3). The mechanism of action of Darzalex®, facilitated by its active compound daratumumab, involves binding to the CD38 protein, which is prominently expressed on the surface of MM cells. By targeting CD38, daratumumab triggers an immune-mediated cytotoxic response, leading to the elimination of malignant plasma cells (4).

However, the use of Darzalex® poses challenges in pre-transfusion testing due to its strong binding affinity of the monoclonal anti-CD38 antibody to CD38 protein, resulting in panreactivity with test erythrocytes and complicating the detection of erythrocyte alloantibodies (5,6).

This potential issue is of significant concern since pre-transfusion testing is essential for preventing transfusion reactions resulting from incompatible blood transfusions, including potentially life-threatening hemolytic reactions. Specific immunohematological testing procedures are necessary to address the interference caused by the monoclonal antibody anti-CD38.

The objective of this case report is to outline the procedures, significance, and methodologies for mitigating this interference using the DaraEx® reagent. Additionally, we

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will delineate the advantages of this approach, comparing it to conventional methodologies previously employed in the field.

CASE REPORT

We present the cases of three patients diagnosed with MM and treated with Darzalex® at our institution in 2023. Among them, two patients were male, and one patient was female, with ages ranging from 44 to 71 years.

Through effective collaboration with clinicians, all patients were referred for immunohematological testing before medication administration.

The testing included blood typing, indirect antiglobulin test (IAT), direct antiglobulin test (DAT), and cross-matching tests due to the need for red blood cell (RBC) transfusion preparations. There were no issues in determining blood groups, and the analysis was performed using the Eriythra automated system (Grifols, Spain), while IAT was performed using polyspecific coombs (IgG + C3d) gel cards (Bio-rad, Switzerland). All IAT and DAT tests conducted before drug administration yielded negative results.

However, following the administration of Darzalex®, all three patients exhibited positive results on IAT (Figure 1). Cross-matching tests conducted with RBC concentrates also yielded positive results, with strengths ranging from 2+ to 3+.

To eliminate interference, we used a specific DaraEx® reagent that utilizes Fab fragments of anti-CD38 to mitigate interference by masking CD38 on the cell surface. This approach avoids nonspecific panreactivity and neutralizes anti-CD38 (7). Subsequent application of this reagent resulted in negative IAT results for all three patients (Figure 2). However, one patient still displayed a weakly positive cross-matching test (<1+), suggesting that complete elimination of interference may not always be achievable with the DaraEx® method.

After discovering that our patient with a weak cross-match received medication that same day, we consulted hematologist regarding the urgency of transfusion. Consequently, the administration of blood products has been postponed until retesting, following a decrease in the medication's blood concentration.

Despite the limitations of employing the DaraEx® method in the initial days following Darzalex® administration, we successfully transfused all three patients with RBC concentrates on multiple occasions, without any recorded post-transfusion reactions. All three patients were followed up to 6 months after the last transfusion with antibody screening. None of the patients developed alloantibodies during the 6-month follow-up.

DISCUSSION

Monoclonal antibody anti-CD38 causes pan-reactivity with test erythrocytes ranging from 1+ to 3+ in all methods performed in IAT as well as in all techniques (tube, microcolumn, or solid phase). The strength of the reaction correlates with the time elapsed since the last dose of Darzalex®, and testing disturbances can persist for up to 6 months following the last drug administration (8). Given the severity of MM, the demand for transfusions in patients treated with

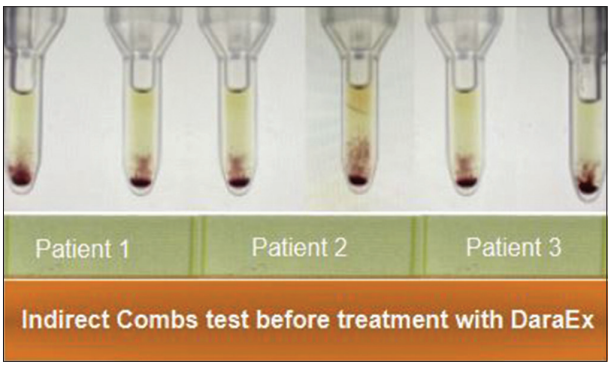

FIGURE 1. Panreactivity observed before treating reagent red blood cells with DaraEx®.

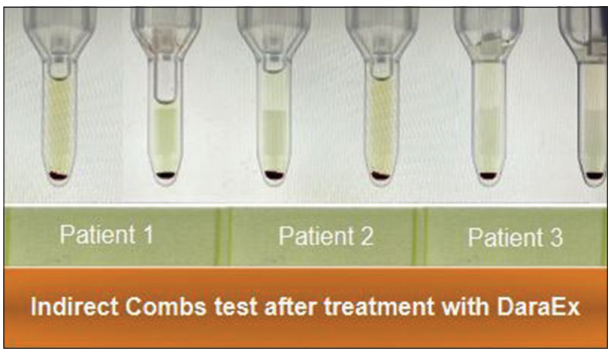

FIGURE 2. Successfully removed panreactivity after treating reagent red blood cells with DaraEx®.

the monoclonal antibody anti-CD38 is substantial, ranging from 30% to 80% (9). Therefore, the American Association of Blood Banks recommends informing the transfusion service about the initiation of Darzalex® treatment (10).

Since the discovery of the interference caused by Darzalex® in pre-transfusion testing, various removal methods have been tested. Some methods have proven insufficiently effective, while others were highly complex and required specialized personnel, resulting in significant costs.

Presently, two methods are predominantly used worldwide: Erythrocyte treatment with dithiothreitol (DTT) and the DaraEx® reagent, as well as combinations of these two methods. DTT treatment of erythrocytes has long been regarded the most effective method, given its widespread use and availability in many laboratories. Multiple studies have demonstrated that Darzalex® interference with blood matching can be effectively mitigated by utilizing RBC treated with DTT. It denatures the CD38 antigen and prevents antibody binding by cleaving the disulfide bond on the CD38 receptor. However, DTT also denatures other RBC antigens in addition to CD38, predominantly the Kell antigen, which may complicate the selection of appropriate blood products (11). Transfusion of blood products that are Kell antigen negative is recommended. In contrast to DTT, DaraEx® reagens does not induce denaturation and demonstrates superior results in practice, as well as in studies conducted by other authors.

The study conducted by Raos and colleagues demonstrated that after treatment with DTT, interference in cross-reaction was successfully eliminated in 60% of cases. However, when using the DaraEx® reagent, interference

was successfully removed in 78% of cases (8). Even better results were achieved by Habicht and colleagues, who reported that DaraEx® effectively mitigated the interference caused by anti-CD38 antibodies in 86% of patient samples tested, while DTT was successful in only 68% of cases. They also emphasized that unlike DTT, DaraEx® does not negatively impact sensitive blood group systems (7).

The emergence of Darzalex® as a therapeutic option for MM has revolutionized treatment strategies for this malignancy. Our case report highlights the importance of addressing potential challenges associated with Darzalex® therapy, particularly regarding its impact on pre-transfusion testing procedures. The implementation of a comprehensive quality system in transfusion medicine and accurate laboratory testing is of utmost importance, and continuous improvement should be the goal (12).

CONCLUSION

Protocols need to be established to ensure the safety and efficacy of laboratory testing in addressing interference in pre-transfusion testing and selecting RBC products. Close collaboration between clinicians and transfusion departments is crucial to mitigate interference and uphold the highest standards of patient care. Patients undergoing Darzalex® therapy should undergo comprehensive immunohematological testing prior to medication administration. This testing should include the identification of clinically significant erythrocyte antigens and determination of antiglobulin tests. In transfusion medicine, it is crucial to administer RBC products that are matched for clinically significant antigens within the Rh, Kell, Kidd, Duffy, and MNS blood group systems. This practice significantly reduces the risk of hemolytic transfusion reactions by over 90%. Given the increased need for blood transfusions in MM patients, ensuring the compatibility of blood products is essential for safe transfusion practices.

DECLARATION OF INTERESTS

Authors declare no conflict of interests.

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