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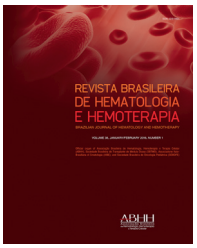

Original article

Transfusion management for patients taking an anti-CD38 monoclonal antibody

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ABSTRACT

Introduction: Pre-transfusion tests, essential for the release of blood components, may be affected by drugs. Monoclonal antibodies represent a class of medications increasingly used in the clinical practice, with anti-CD38 monoclonal antibodies (daratumumab) being a promising resource in the treatment of refractory myeloma. This monoclonal antibody recognizes CD38 in myeloma cells and interferes with pre-transfusion tests by causing panreactivity in indirect antiglobulin tests thereby clinically masking alloantibodies. Dithiothreitol is a reagent that breaks disulfide bonds and effectively destroys antigenic sites for CD38 on red blood cells. This study reports the immunohematological findings of pre-transfusion tests of patients with multiple myeloma receiving daratumumab and on solutions to prevent the interference of this monoclonal antibody.

Methods: Serum samples from five patients on anti-CD38 monoclonal antibody treatment were evaluated. Tests performed included ABO/RhD typing, indirect antiglobulin test, direct antiglobulin test and eluate test. A daily evaluation was performed to determine the shelf life of dithiothreitol-treated red blood cells when stored in Alsever's solution.

Results: No interference in the ABO/RhD typing results was noted but in all samples, a panreactivity was observed in indirect antiglobulin tests. Regarding the direct antiglobulin test, two samples presented positive results but negative eluates. In all samples, treatment of reagent red blood cells with 0.2 M dithiothreitol offset interference by anti-CD38 monoclonal antibodies. Dithiothreitol-treated red blood cells stored in Alsever's solution were stable for up to 15 days.

Conclusion: Treatment of reagent red blood cells with dithiothreitol can be efficient and accessible to offset the interference of the anti-CD38 drug in pre-transfusion tests. The number of costly serological workups can be reduced by having stored dithiothreitol red blood cells with this proving to be a useful reagent for investigating anti-CD38.

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Introduction

The interference of drugs in pre-transfusion tests is a well-known phenomenon in the blood bank routine. The difficulty in handling these interferents was initially described in the 1970s in respect to drugs and chemicals used as antibiotics, antihypertensives and analgesics. Over the years, the number of interfering drugs has increased in association with developments in the pharmaceutical industry.[1]

Among the etiological mechanisms, the immune complex formation, drug adsorption in the erythrocyte membrane, autoantibody formation and modifications of the erythrocyte membrane are described.[2,3] The major concern related to the presence of these interferents is the possible impact on the transfusional management of patients using these drugs. Discrepant tests induced by the presence of interferents may generate erroneous interpretations and lead to delays in the release of blood components.[4]

Monoclonal antibodies (MoAbs) represent a class of therapy that is increasingly used in a variety of pathological conditions, including solid tumors, leukemia, and infections.[5] Daratumumab (anti-CD38) is an immunoglobulin (Ig)G1 MoAb that is indicated in the treatment of relapsed/refractory multiple myeloma[6] and has shown high efficiency and safety as described by Dimopoulos et al. in the POLLUX study.[7] Daratumumab is directed to the CD38 portion of malignant cells; however, this drug reacts with the red blood cell (RBC) reagents used in pre-transfusion tests which also express CD38 on their cell surface complicating the identification of clinically significant RBC antibodies[8] since the plasma/serum will be panreactive with IAT screening and panel cells. Mild hemolysis has been associated with this drug, with a maximum hemoglobin drop of 1.0 g/dL (related to splenic sequestration of RBCs with surface-bound anti-CD38). These alterations identified in pre-transfusion tests may persist for months making transfusional management of these patients even more difficult.[9] The American Association of Blood Banks (AABB) issued a bulletin suggesting strategies for blood banks to effectively bypass daratumumab panreactivity findings that include chemical treatments of panel cells, the use of a cord blood cell panel and inactivation of anti-CD38 in the patient's plasma through the use of soluble human CD38.[10]

Dithiotreithol (DTT), a disulfide-bridging reductant reagent is commonly used in blood banks and has been applied as an affordable and efficient resource to resolve this identified panreactivity through the destruction of antigenic sites for CD38 on red blood cells.[11,12] However, DTT is known to denature antigens from the Kell blood group system and other blood group antigens found less commonly in the population.[13] Other alternative and promising solutions, such as the use of cord blood cells[14] and, neutralization of free daratumumab in plasma, are not yet widely available.[9,11] Assertive strategies should be applied for the safe release of blood components and to avoid possible predictable transfusion complications.

This study describes the immunohematological findings of pre-transfusion tests on patients receiving anti-CD38 MoAbs and evaluates the use of DTT as a laboratory strategy to eliminate the interference of this drug by removing CD38 from the RBC surface. Although DTT may be effective, it is time-consuming and therefore this study also aimed to evaluate the storage survival of DTT-treated reagent RBCs to mitigate the laborious work of DTT cell treatment prior to each transfusion.

Methods

Patient samples

Pre-transfusion samples of five hematological patients with diagnosis of multiple myeloma receiving anti-CD38 drugs were sent to the immunohematology reference laboratory for serologic testing from January to December 2016. Information regarding the gender and age of the patient and the time between anti-CD38 MoAb infusion and sample collection were also sent to the laboratory.

Serologic testing

Serologic testing included ABO/RhD typing, antibody screening, RBC panel, direct human antiglobulin test (DAT), and antihuman globulin (AHG) cross-match in gel test (Grifols, Spain). If the DAT was positive, an eluate test was performed.

Antibody identification was performed using commercial panels of 11 cells previously phenotyped for the main erythrocyte antigens (Bio-Rad, Brazil; Grifols, Spain). DAT was performed with polyspecific and monospecific testing for IgG and C3 (DC screening, Grifols, Spain). Eluates were prepared from patient samples with a positive DAT using an acid elution technique (Diacidel, Bio-Rad, Switzerland).

Serum samples showing panreactivity with IAT screening and panel cells were further tested with reagent RBCs treated with 0.2 M DTT solution. Briefly, 0.2 mol/L DTT was prepared by diluting 1 g DTT (Sigma–Aldrich, São Paulo) in 32 mL of phosphate buffered saline (PBS – pH: 8.0). RBCs positive for the k+ and E antigens were used as positive and negative controls to verify the efficacy of DTT treatment. A volume of reagent RBCs were washed three times with saline, diluted to a 3% suspension with PBS (pH: 7.3), mixed with four volumes of 0.2 mol/L DTT and incubated at 37 °C for 20 min. RBCs were then subjected to a final wash sequence with PBS for subsequent testing.

Molecular testing

DNA was extracted from whole blood using the QIAmp DNA blood mini-kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. Molecular tests were performed on all samples using the human erythrocyte antigen (HEA) BeadChip™ assay (Bioarray Solutions, Immucor, NJ, USA). Genotypes and predicted phenotypes were determined.

Storage survival of dithiotreithol-treated red blood cells

A daily evaluation was performed in order to determine the shelf life of DTT-treated reagent RBCs when stored in Alsever solution. The study was conducted over a period of 15 days. Four screening RBCs with the Rh phenotypes: $R_1{}^{W}R_1$, R_2R_2, rr and R_1R_1 from Grifols (Serascan Diana 4 reagent) were treated

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