BLOOD TRANSFUSION MANAGEMENT FOR PATIENTS WITH MULTIPLE MYELOMA TREATED WITH ANTI-CD38 MONOCLONAL ANTIBODIES – CASE REPORTS

TRANSFUZIOLOŠKO ZBRINJAVANJE PACIJENATA SA MULTIPLIM MIJELOMOM LEČENIH ANTI-CD38 MONOKLONSKIM ANTITELIMA – PRIKAZI SLUČAJEVA

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Case report
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Abstract

Introduction. Daratumumab is a monoclonal antibody targeting CD38, commonly used in the treatment of newly diagnosed and relapsed multiple myeloma. The expression of CD38 on red blood cells poses a challenge as anti-CD38 can interact with red blood cells during the indirect antiglobulin test, complicating pre-transfusion testing and delaying the availability of antigen-negative blood units. **Case Report.** The first case involved a 49-year-old woman with anemia secondary to multiple myeloma, who had received treatment with Darzalex® three months prior. The second case was a 66-year-old woman with relapsed multiple myeloma, undergoing treatment with Darzalex®, who required a blood transfusion as part of her therapeutic protocol. Both patients' blood samples demonstrated complications during pre-transfusion testing, including panagglutination of red blood cells during the indirect antiglobulin test, affecting both antibody screening and cross-matching procedures. Following treatment of the red blood cells with Dithiothreitol, the indirect antiglobulin test results were rendered negative. However, since dithiothreitol destroys the Kell blood group antigen, both patients received Rh- and Kell-matched blood units to ensure compatibility. **Conclusion.** Dithioerythritol remains the most commonly available and effective method for resolving pre-transfusion testing issued in patients undergoing anti-CD38 monoclonal antibody therapy. Ensuring antigen matching patient for clinically significant blood group antigens between patient and donor red blood cells is crucial. Future efforts should focus on enhancing coordination between clinical teams and blood transfusion laboratories, developing unified guidelines, and investing in advanced testing modalities to overcome these transfusion challenges.

Key words: Blood Transfusion; Multiple Myeloma; Antibodies, Monoclonal; Antineoplastic Agents; Coombs Test; Genotyping Techniques

Sažetak

Uvod. Daratumumab je monoklonsko antitelo usmereno na CD38 i koristi se za lečenje novodijagnostikovanog i relapsirajućeg multiplog mijeloma. Zbog ekspresije CD38 na eritrocitima, ova antitela raguju sa eritrocitima koji se koriste za indirektni antiglobulinski test ometajući pretransfuzijsko testiranje i otežavajući pravovremeno obezbeđivanje antigen-negativnih jedinica krvi. **Prikaz slučaja.** Prvi pacijent je ženska osoba stara 49 godina, sa kliničkom manifestacijom anemije kao komplikacije multiplog mijeloma. Prošlo je tri meseca od kako je završila terapiju *Darzalex®*-om. Drugi pacijent je 66 godina stara žena sa relapsom multiplog mijeloma, kojoj je utvrđena potreba za transfuzijom krvi tokom terapije *Darzalex®*-om u sklopu odgovarajućeg protokola. Kod obe pacijentkinje su uzorci krvi pokazali smetnje u pretransfuzijskom testiranju koje je karakterisala panaglutinacija sa test-eritrocitima kod indirektnog antiglobulinskog testa, kako u skriningu antitela tako i kod krosmeča. Nakon što su eritrociti tretirani ditiotreitolom, andirektni antiglobulinski test je postao negativan. Međutim, s obzirom da ditioeritritol uništava antigen *Kell* krvne grupe, oba pacijenta su primila jedinice krvi kompatibilne sa njihovim *Rh* i *Kell* fenotipom. **Zaključak.** Primena ditioeritritola je najčešći, širokodostupan i efikasan metod za rešavanje problema tokom pretransfuzijskog testiranja kod pacijenata na terapiji anti-CD38 monoklonskim antitelima. Značajno je za pacijente obezbediti jedinice eritrocita koje su podudarne na klinički značajne antigene iz krvnogrupnih sistema. Koordinacija između klinika i laboratorija za transfuziju krvi, uspostavljanje jedinstvenih smernica i ulaganje u nove modalitete testiranja biće ključni za rešavanje ovih izazova u budućnosti.

Ključne reči: transfuzija krvi; multipli mijelom; monoklonska antitela; antineoplastični agensi; antiglobulinski test; genotipizacija

Introduction

Multiple myeloma (MM) is a type of hematologic cancer that originates in plasma cells, which are essential component of the immune system. These malignant plasma cells accumulate in the bone marrow, leading to a variety of health complications, including bone lesions, anemia, kidney dysfunction, and compromised immunity [1]. Despite advances in treatment, MM remains an incurable disease, highlighting the need for continuous research into novel therapeutic approaches. One of the most promising strategies

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Abbreviations

MM – multiple myeloma
mAbs – monoclonal antibodies
IAT – indirect antiglobulin test
RBCs – red blood cells
BTIV – Blood Transfusion Institute of Vojvodina
DAT – direct antiglobulin test
DTT – dithiothreitol
UCSS – University Clinical Center of Serbia

in recent years has been the use of monoclonal antibodies (mAbs), which have transformed the treatment landscape for MM, significantly improving patient outcomes [2, 3]. These therapies target specific antigens on myeloma cells, inducing their destruction through mechanisms like immune activation and direct cytotoxic effects. While the introduction of mAbs, particularly those targeting CD38, has marked a significant advancement in MM therapy, it has also presented new challenges in the management of blood transfusions – a critical component of supportive care for many MM patients. Anti-CD38 monoclonal antibodies, such as daratumumab and isatuximab, can bind to CD38 antigens that are expressed at low levels on red blood cells (RBCs) [4]. This binding interferes with antibody screening and crossmatching tests by causing panagglutination in the Indirect Antiglobulin Test (IAT) [4, 5]. Such interference complicates the detection and identification of alloantibodies, as well as the provision of antigen-negative blood, which is vital for maintaining transfusion safety. This issue is particularly significant for MM patients who often require multiple transfusions throughout their treatment, thereby increasing the risk of alloimmunization and subsequent hemolytic transfusion reactions. In this report, we describe two cases involving complex compatibility testing in patients with multiple myeloma undergoing mAbs therapy, and we outline the strategies employed to address these challenges and ensure the safe administration of transfusions.

Case Report

The first case concerns a 49-year-old woman admitted to the Clinic of Hematology at the University Clinical Center of Vojvodina with clinical manifestations of anemia, a complication of her underlying multiple myeloma. The patient had no prior history of blood transfusions. Pretransfusion testing, conducted by the Blood Transfusion Institute of Vojvodina (BTIV), included the following steps to ensure the selection, matching, and reservation of appropriate red cell components for the transfusion recipient: 1) Blood Typing: The patient's blood group was identified as type A, RhD-positive, with Rh phenotype CcDee and negative for the Kell antigen; 2) Crossmatch Testing: A crossmatch was performed using the patient's serum against a sample of RBCs from the selected transfusion unit. The crossmatch involved incubation at 37°C and an antiglobulin phase, and was conducted on commercial Liss/Coombs card with a gel matrix containing anti-IgG and anti-C3d (Diamed GmbH, Switzerland). The result was positive. Further testing included antibody screening by IAT using commercial reagent RBCs (ID-DiaCell I+II, Bio-Rad, DiaMed GmbH, Switzerland) with Liss/Coombs cards (DiaMed GmbH, Switzerland), which returned a positive result with 1+ agglutination (grading 1-4). However, when the same reagent RBCs were enzyme-treated, the antibody screening was negative. The direct antiglobulin test (DAT) and auto control were also negative. Antibody identification using an 11-cell panel (Bio-Rad Diamed GmBH, Switzerland) revealed panreaction with 1+ agglutination. Upon consultation with the hematology team, it was confirmed that the patient had received Daratumumab (Darzalex) three months earlier as part of the DRd protocol (darzalex, lenalidomide, dexamethasone). After treating the RBCs from the transfusion unit with dithiothreitol (DTT), the crossmatch test turned negative. Consequently, the patient was transfused with Rh- and Kell-matched RBC units.

The second case involves a 66-year-old woman who was admitted to the Bone Marrow Transplantation Department of the Clinic of Hematology at the University Clinical Center of Serbia (UCCS) for ongoing treatment of multiple myeloma following autologous hematopoietic stem cell transplantation. The patient reported fatigue and bone pain localized in the cervical and lumbosacral spine, shoulders, and hips. A complete blood count indicated the need for a blood transfusion. The patient was receiving Darzalex as part of her therapeutic regimen. Pretransfusion testing was carried out at Hospital Blood Bank, Department of Pretransfusion Testing in the Emergency Center of UCCS. Blood typing identified the patient as type A, RhD-positive, using DiaMed ID-Gel Card (Diaclon ABO/D + reverse grouping, BioRad, Switzerland) on an automated immunohematology analyzer (IH-1000, BioRad, Switzerland). Crossmatches performed using commercial Liss/Coombs cards (Diamed GmbH, Switzerland) were all positive. Antibody screening by the IAT method, using commercial reagent RBCs (ID-DiaCell I+II, Bio-Rad, DiaMed GmbH, Switzerland), showed a 2+ reaction, while the DAT and auto control were negative. Antibody identification with an 11-cell panel (Bio-Rad Diamed GmBH, Switzerland) displayed panreaction with 2+ agglutination. Given that the UCCS information system confirmed the patient's ongoing

mAbs therapy, the panagglutination was attributed to the effect of the therapy. Subsequently, the patient's Rh and Kell phenotypes were determined, and a compatible RBCs unit was successfully provided.

Discussion

Panagglutination occurs when a patient's serum reacts with all RBCs used in both antibody screening and identification panel cells. Recently, this phenomenon has become increasingly prevalent in transfusion services, particularly among patients with multiple myeloma undergoing mAbs therapy [6]. Anti-CD38 mAbs bind to CD38 antigens present on the surface of RBCs, resulting in interference with routine pretransfusion testing procedures [7, 8]. The CD38 protein is also expressed on various lymphoid and myeloid cells, as well as certain non-hematopoietic cells [9]. Western blot analyses of CD38 on human RBCs have demonstrated an increased expression of CD38 on the membranes of RBCs in patients with tumors, compared to its lower expression in healthy individuals [10]. It is suggested that cytokines secreted by cancer cells might induce this heightened CD38 expression [10, 11]. The presence of these antibodies can lead to false-positive results in crossmatching and antibody screening, complicating the identification of clinically significant alloantibodies. Anti-CD38 mAbs cause panreactivity with commercial reagent RBCs, showing agglutination strengths ranging from 1+ to 3+ in screening or antibody identification tests using the IAT. The intensity of this reaction depends on the time elapsed since the last dose of Darzalex, with interference potentially lasting up to six months after the last administration [12]. In our cases, pretransfusion testing conducted within six months of the last dose revealed agglutination strengths of 1+ and 2+ using Liss/Coombs cards.

While the reactions caused by anti-CD38 mAbs can resemble those of autoantibodies, other diagnostic tests such as autocontrol, DAT, and eluate, are often negative, which may lead to the mistaken assumption that it is an alloantibody against a high-frequency antigen [9]. To prevent adverse transfusion events, several strategies should be considered. Ideally, before initiating mAb therapy, patient samples should be sent to the transfusion service for comprehensive testing, including ABO/RhD group typing, antibody screening, DAT, and phenotyping or genotyping (if patient received transfusion up to three months before) for Rh (CcEe), Kell, Kidd, Duffy, and Ss antigens [9, 12]. Unfortunately, blood samples are often only collected after the administration of mAb therapy, leading to interference with pretransfusion testing. When pretransfusion testing is affected by ongoing or recent mAb therapy, DTT treatment of RBCs is the most commonly used method to reduce interference in IAT [13]. DTT denatures the CD38 antigen on RBCs, preventing anti-CD38 antibodies from binding and causing agglutination [14]. However, this approach also destroys Kell antigens, which potentially complicates the detection of anti-K alloantibodies, necessitating the consideration of K-negative blood for transfusion [13, 14]. Moreover, DTT treatment is a time-intensive process, typically requiring 2-4 hours to complete. Hosokawa et al. have made a notable contribution by reducing the time required for antibody screening and cross-match. They achieved this by lowering the DTT concentration from 0.2 mol/L to 0.01 mol/L and employing an IAT tube technique with an automated cell washing centrifuge [15]. This modification also reduces the extent of K antigen denaturation.

An alternative strategy involves masking CD38 on the RBC surface using the DaraEx reagent, which contains anti-CD38 antibodies without the human Fc region [12]. When RBCs are treated with the DaraEx, the reagent binds to CD38 and blocks the epitopes to which Darzalex would typically attach. Tenorio et al. demonstrated that its effectiveness of DarEx is compatible to that of DTT treatment, with the added advantage of being simpler and faster [12]. However, this reagent is not yet available in Serbia. In cases where panagglutination persists despite treatment or reagent modification, RBC phenotyping or molecular genotyping can be utilized to assess the risk of alloimmunization [16]. This approach is particularly valuable for patients who may have developed alloantibodies before the initiation of mAb therapy.

Conclusion

Panagglutination in multiple myeloma patients undergoing monoclonal antibody therapy, particularly with agents like Darzalex, poses a significant challenge in pretransfusion testing. The non-specific agglutination triggered by these therapies can lead to delays in transfusion, obscure the detection of clinically significant alloantibodies, and increase the risk of transfusion-related complications. Although current strategies – such as dithiothreitol treatment, the use of DaraEx reagent, and genotyping – provide some solutions, further research is crucial to enhance patient safety. Close collaboration between clinics and blood transfusion laboratories, the establishment of standardized guidelines, and investment in innovative testing methods will be the key to overcoming these challenges in the future.

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