

# Interference Analysis of Monoclonal Antibody Cluster of Differentiation 38 on ABO Blood Group Identification and Cross-Matching

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We attempt to analyze and adopt the interference of monoclonal antibody cluster of differentiation 38 on ABO blood group identification and cross-matching. Search PubMed, Medline, Web of Science, China National Knowledge Infrastructure, Wanfang and other domestic and foreign databases, screening of patients requiring blood transfusion after receiving anti-cluster of differentiation 38 monoclonal antibody, retrospective analysis of anti-human globulin cassette method for antibody screening and cross-matching of serum from patients treated with cluster of differentiation 38 monoclonal antibody. According to the search results, a total of 185 patients who received cluster of differentiation 38 as monotherapy or combination therapy and required blood transfusion were retrieved. Among them, 98 cases of multiple myeloma, 22 cases of chronic lymphocytic leukemia and 16 cases of relapsed acute myeloid leukemia, total was 136 cases. But among the 124 patients who received daratumab treatment, a total of 49 patients (39.5 %) received 236 blood transfusions during treatment. Among these, 47 patients (37.9 %) received 147 red blood cell infusions, 17 patients (13.7 %) received 89 platelet transfusions. Among the systemic lupus erythematosus patients, there was only one case of transfusion-related reactions after platelet (rather than red blood cell) transfusion and no other adverse reactions. In the investigation of multiple bone marrow-related diseases, we found that 5 cases developed indirect antiglobulin test and were weakly positive, all patients did not see any discrepancies in ABO blood type identification. Antibody identified panagglutination occurred in only 1 patient with multiple myeloma. Among the multiple myeloma patients, cluster of differentiation 38 possessed a low expression on the surface of erythrocytes and its level on erythrocytes does not differ between individuals. After anti-cluster of differentiation 38 injections, macrophages increased, i.e. the antigen of cluster of differentiation 38 molecules in the patient's own erythrocyte falls off. Cluster of differentiation 38 monoclonal antibody substantially made no interference with ABO, rhesus or extended antigen matching. In antibody screening and cross-matching, cluster of differentiation 38 monoclonal antibody caused interference only at indirect antiglobulin test, showing antibody agglutination intensity 1<sup>+</sup> or weaker reactivity. Hematological diseases such as multiple myeloid in antibody screening and cross-matching, anti-cluster of differentiation 38 antibody only caused interference in indirect antiglobulin test, showing weaker reactivity; cluster of differentiation 38 monoclonal antibody substantially made no interference with ABO, rhesus or extended antigen matching.

**Key words:** Blood transfusion, monoclonal antibody cluster of differentiation 38, itching, daratumumab, apoptosis

Cluster of Differentiation 38 (CD38) is a receptor which had high expression on the surface of Multiple Myeloma (MM) cells; it has a variety of functions, included signal transduction, receptor-mediated adhesion and enzymatic activity. Daratumumab is a human Immunoglobulin G1 Kappa (IgG1κ) monoclonal

antibody against CD38, it has been proved to have remarkable clinical curative effect in treating patients with previous MM<sup>[1,2]</sup>. Antitumor activity mediated by daratumumab is activated by several CD38 immune mechanism-mediated (e.g. complement-dependent cytotoxicity, antibody dependent cytotoxicity, antibody

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dependent phagocytosis), apoptosis and CD38 enzymatic activity regulation<sup>[3,4]</sup>. Recently, daratumumab was proved to reduce the immunosuppressive function of CD38 myeloid-derived suppressor cells, regulatory T cells and regulatory B cells and then increased clonality of T cell<sup>[5,6]</sup>. In 2015, daratumumab has got approval in United States and elsewhere in previously treated MM patients, it can be adopted as monotherapy or combined application with bortezomib and dexamethasone or lenalidomide and dexamethasone<sup>[7,8]</sup>.

Approved application of daratumab for monotherapy is on account of the safety and efficacy demonstrated in two clinical studies-GEN501 and Sirius. During the study of above projects, routine blood screening in blood banks showed consistently positive Indirect Anti-human globulin Test (IAT) results among patients who received daratumab therapy<sup>[9,10]</sup>. IAT, also called indirect Coombs test, typically used to test Red Blood Cell (RBC) alloantibody compatibility in plasma prior to transfusion<sup>[11,12]</sup>. Since CD38 is expressed on human erythrocytes, daratumumab may interfere with IAT by binding to endogenous CD38 present on the surface of RBC<sup>[12,13]</sup>. In relapsed and refractory MM treatment, patients often have anemia and frequent need for blood transfusions, therefore, find and establish a blood group antibody screening and cross-matching program that excludes anti-CD38 monoclonal antibody interference has become an urgent problem to be solved in the blood transfusion department.

This study intends to analyze the cases of pre-transfusion detection of patients using CD38 monoclonal antibody (daratumumab) treatment in relevant literatures at home and abroad, analyzed various cases and then summarized the interference of pre-infusion blood typing in daratumumab-treated patients, antibody screening and cross-matching detection, in order to provide more theoretical reference for blood transfusion examination in patients treated with CD38 monoclonal antibody.

## MATERIALS AND METHODS

### Literature search:

In 2015, daratumab became the first anti-CD38 monoclonal antibody approved by the United States Food and Drug Administration (USFDA), so the retrieval time is set to 'January 2015 to March 2022'. Chinese literature retrieval takes 'CD38 monoclonal antibody' and 'blood transfusion' as the search words and searches in Wanfang data, China National Knowledge Infrastructure (CNKI), VIP information

database and other Chinese databases to obtain relevant literature. English literature retrieval takes 'anti-CD38' and 'fusion' as the search words and searches in foreign language databases such as PubMed, Medline and Web of Science.

### Literature inclusion criteria:

Through the preliminary screening of literature abstracts, we can obtain the full text, exclude the review, select the relevant literature with case report. Further analyze the cases and eliminate the cases with incomplete case report information.

### Research target:

Blood transfusion cases in clinical trials of CD38 monoclonal antibodies obtained from literature searches in Chinese and English databases.

### Statistical analysis:

Collated and collected information from the included case reports, the source of the case, the patient's primary disease, medication, methods and results of pre-transfusion testing, statistically analyzed the interference and treatment measures of CD38 monoclonal antibodies on pre-transfusion detection and advised to eliminate anti-CD38 monoclonal antibodies interference on detection before transfusion.

## RESULTS AND DISCUSSION

According to the search results, a total of 136 patients who received CD38 as monotherapy or combination therapy and required blood transfusion were retrieved, their hemoglobin  $\leq 7$  g/dl. Among them, 98 cases of MM, 22 cases of chronic lymphocytic leukemia and 16 cases of relapsed acute myeloid leukemia as shown in Table 1. CD38 monoclonal antibody is daratumab<sup>[14-18]</sup>.

**TABLE 1: INCLUDED TRANSFUSION PATIENT INFORMATION**

Cases	Disease type	Constituent ratio (%)
98	MM	72.05
22	Chronic lymphocytic leukemia	16.17
16	Relapsed acute myeloid leukemia	11.76

In addition to daratumab (Janssen Biotech), other anti-CD38 drugs currently in Phase 1 or 2 clinical trials include MOR202 (MorPhoSys), isatuximab (Sanofi-Aventis) and TAK-079 (Takeda), which were adopted for systemic lupus erythematosus or other autoimmune diseases treatment. Literature research shows that

only patients with systemic lupus erythematosus receive blood transfusion, among the 124 patients with systemic lupus erythematosus who received 8 mg/kg or 16 mg/kg daratumab, a total of 49 patients (39.5 %) received 236 blood transfusions during treatment as shown in Table 2. Among these, 47 patients (37.9 %) received 147 RBC infusions, 17 patients (13.7 %) received 89 platelet transfusions, a total of 49 patients with blood transfusion (some patients received both RBC and platelets). Among the above patients, there was only one case of transfusion-related reactions after platelet (rather than RBC) transfusion. Hemolysis and other adverse blood transfusion reactions, not yet reported<sup>[19,20]</sup>.

IAT detected after daratumumab in 2 of 90 patients with MM, IAT detected after daratumumab in 1 of 22 patients with chronic lymphocytic leukemia, IAT detected after daratumumab in 1 of 16 patients with relapsed acute myeloid leukemia. 0 cases of discrepancy between positive and negative results of ABO blood type identification in all patients. Antibody identified panagglutination in only 1 patient with MM as shown in Table 3.

Table 4 showed RBC CD38 and CD47 expressions and the interference profile observed by anti-CD38

(daratumab) or anti-CD47 (Hu5F9-G4). CD38 expression was low but CD47 was high on the surface of erythrocytes. CD47 expression changed complying with Rhesus (Rh) phenotype. CD38 expression levels on erythrocytes possessed no difference between individuals. After CD38 monoclonal antibody injection, macrophages increased, i.e. the antigen of CD38 molecule in the patient's own erythrocyte falls off. However, there was no loss of CD47 after CD47 monoclonal antibody treatment. CD38 monoclonal antibody was different from CD47 monoclonal antibody in immunoglobulin subclasses and CD38 monoclonal antibody substantially had no interference with ABO, Rh or extended antigen matching, but CD47 monoclonal antibody caused strong interference in antibody screening and identification. Moreover, the patient's large numbers of anti-CD47 coated erythrocytes spontaneous agglutination may sometimes lead to false positives for ABO, Rh (DCEce) or expanded antigen. In antibody screening and cross-matching, anti-CD38 caused interference only in IAT, showing antibody agglutination intensity 1<sup>+</sup> or weak reactivity. Oppositely, anti-CD47 caused interference at all stages of detection, resulting in computer cross-matching interference and exhibited 3<sup>+</sup> to 4<sup>+</sup> reactivity<sup>[21]</sup>.

**TABLE 2: TRANSFUSION INFORMATION FOR PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS TREATED WITH DARATUMAB**

	8 mg/kg		16 mg/kg		Total	
	Blood transfusion times	Blood transfusion subjects, n (%)	Blood transfusion times	Blood transfusion subjects, n (%)	Blood transfusion times	Blood transfusion subjects, n (%)
	18		106		124	
Blood transfusion type	43	7 (38.9)	193	42 (39.6)	236	49 (39.5)
Whole blood	0	0	0	0	0	0
RBC	21	7 (38.9)	126	40 (37.7)	147	47 (37.9)
Fresh freezing plasma	0	0	0	0	0	0
Platelet	22	3 (16.7)	67	14 (13.2)	89	17 (13.7)

**TABLE 3: PRE TRANSFUSION TEST RESULTS OF PATIENTS USING CD38**

Antigen and antibody tests type	Number of people	Percentage
ABO blood type identification does not match the positive and negative	0	0
Indirect anti-human ball positive ITA	4	0.0313
Antibody identification complete agglutination	1	0.0078

**TABLE 4: COMPARISON OF ERYTHROCYTE EXPRESSION AND PRE-TRANSFUSION INTERFERENCE CHARACTERISTICS BEFORE AND AFTER ANTI-CD38 (DARATUMAB) AND ANTI-CD47 (HU5F9-G4) TREATMENT**

Testing index	CD38	CD47
Erythrocyte surface antibody expression	Low	High
Epitope/antigen shedding	Yes	No
Subtype	IgG1	IgG4
ABO interference	No	Yes
D and extended antigen matching problem	No	Uncertain
Antibody screening and cross matching interference	Only IAT (1 <sup>+</sup> )	All stages (3 <sup>+</sup> to 4 <sup>+</sup> )

The interference of drugs on pre-transfusion testing is widespread, which seriously affects the process of blood transfusion in patients. Transfusion workers were aware of drug interference before transfusion testing in the 1970s and involved drugs such as antibiotics, antihypertensive, pain relievers and chemicals. For years, as the pharmaceutical industry has grown, the number of interference drugs is mounting up. False positive cross-matching caused by the presence of interfering substances can produce incorrect interpretations, because delayed blood transfusion, which can endanger the patient's life.

Preclinical studies have found that daratumumab has cytotoxicity effects on tumor cells through multiple mechanisms, including complement-dependent cytotoxicity, antibody-dependent cytotoxicity and apoptosis<sup>[22]</sup>. Daratumumab has also shown efficacy in MM treatment in clinical trials, but patients receiving daratumumab often require a large blood supply, therefore, patients need a lot of typing and screening after starting daratumumab treatment to prepare for subsequent blood transfusion. At present, there are few reports in the domestic and foreign literature on the use of daratumab for allogeneic immunization in myeloma patients.

This study found that through a large number of research related literature, 136 blood system related patients who received CD38 as monotherapy or combination therapy and required blood transfusion, their hemoglobin  $\leq 7$  g/dl. Among them, 98 cases of MM, 22 cases of chronic lymphocytic leukemia and 16 cases of relapsed acute myeloid leukemia. CD38 monoclonal antibody is daratumab. In addition to daratumab (Janssen Biotech), other anti-CD38 drugs currently in phase 1 or 2 clinical trials include MOR202 (MorPhoSys), isatuximab

(Sanofi-Aventis) and TAK-079 (Takeda), which were adopted for treating systemic lupus erythematosus or other autoimmune diseases. Literature research shows that in autoimmune diseases, only patients with systemic lupus erythematosus receive blood transfusion, among the 124 patients with systemic lupus erythematosus who received 8 mg/kg or 16 mg/kg daratumab, a total of 49 patients (39.5 %) received 236 blood transfusions during treatment as shown in Table 2. Among these, 47 patients (37.9 %) received 147 RBC infusions, 17 patients (13.7 %) received 89 platelet transfusions. Among the above patients, there was only one case of transfusion-related reactions after platelet (rather than RBC) transfusion. Hemolysis and other adverse blood transfusion reactions, not yet reported.

In the investigation of multiple bone marrow-related diseases, we found that 5 cases had IAT and were weakly positive and no ABO blood type identification was found in all patients. Antibody identified panagglutination only happened in one patient with MM. If IAT happens, the blood bank can conduct Dithiothreitol (DTT) to process sieve-resistant cells and donor RBC, then remove the influence of CD38 monoclonal antibody on antibody screening and cross matching, perhaps most effectively so far. If RBC antibody screening is negative after DTT application, it can be assumed that the patient does not have alloantibodies, taking into account the possible changes in Kell<sup>[23,24]</sup>. The blood bank can cross match the DTT treated Kell negative RBC with patient serum to obtain safe blood. If IAT is positive even after DTT application, this indicates the presence of true alloantibodies, should adopt DTT-treated RBC for antibody identification<sup>[25]</sup>.

Further analyzed the interference profile observed with anti-CD38 (daratumab) or anti-CD47 (Hu5F9-G4) treatment, CD38 expression was low but CD47 was high



on the surface of erythrocytes. CD47 expression changed complying with Rh phenotype. CD38 expression levels on erythrocytes possessed no difference between individuals<sup>[26]</sup>. After CD38 monoclonal antibody injection, macrophages increased, i.e. the antigen of CD38 molecule in the patient's own erythrocyte falls off. However, there was no loss of CD47 after CD47 monoclonal antibody treatment. CD38 monoclonal antibody was different from CD47 monoclonal antibody in immunoglobulin subclasses and CD38 monoclonal antibody substantially had no interference with ABO, Rh or extended antigen matching, but CD47 monoclonal antibody caused strong interference in antibody screening and identification. Moreover, the patient's large numbers of anti-CD47 coated erythrocytes spontaneous agglutination may sometimes lead to false positives for ABO, Rh (DCEc) or expanded antigen. In antibody screening and cross-matching, anti-CD38 caused interference only in IAT, showing antibody agglutination intensity 1<sup>+</sup> or weak reactivity. Oppositely, anti-CD47 caused interference at all stages of detection, resulting in computer cross-matching interference and exhibited 3<sup>+</sup> to 4<sup>+</sup> reactivity.

Since the first reports on anti-CD38 as well as anti-CD47 interference, there are more different reports on how to deal with this interference and the selection of RBC of a wide range of blood types for transfusion. All reported approaches have advantages and disadvantages and for patients receiving anti-CD38 monoclonal antibody therapy, selection of appropriate RBC may significantly delay transfusion progression. The number of FDA-approved daratumumab indications continues to increase, recently including newly diagnosed, transplant-eligible, previously untreated myeloma patients<sup>[27,28]</sup>. It significantly increased potential for daratumumab in other clinical indications. As a result, the number of patients taking daratumumab and the associated workload in transfusion services may increase. Appropriate and effective management of these patients will become increasingly important in the future. Moreover, hospitals should make agreements to communicate about interference in time with relevant parties (patients, transfusion departments, physicians and other hospitals). Furthermore, the transfusion departments should have agreements on handling interference and selecting compatible RBC.

### Conflict of interests:

The authors declared no conflict of interest.

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