Detection of Anti-CD38 immunotherapy interference with pre-transfusion antibody screening using LISS & Polybrene

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Abstract – *Immunotherapy drugs such as Anti-CD38 (Daratumumab) interfere with pre-transfusion antibody screening tests. The purpose of this present study is to evaluate and compare the results of Qatar-based patients taking anti-CD38 using the Polybrene technique (LIP/LIPAT) and low-ionic-strength saline-indirect antiglobulin test (LISS-IAT) when conducting antibody pre-transfusion screening. Twenty (20) residual plasma samples from patients taking anti-CD38 medication were tested using the LIP/LIPAT and LISS-IAT against Immucor Panoscreen three cells. The results were then compared and graded from 0 to 4+ based on their strength of agglutination. The samples tested using LISS-IAT were positive, with reactions ranging from weak positive to 1+ only in the AHG phase. On the other hand, all samples tested negative using the manual LIP. However, in the LIPAT test, 95% of the samples tested positive microscopically. In conclusion, patients taking immunotherapy drugs such as Anti-CD38 can use the manual Polybrene or LIP as the method of choice in conducting pre-transfusion screening as these yields more accurate results.*

Keywords – *Antibody screening, Anti-CD38 drugs, Immunotherapy, Monoclonal antibody, Polybrene*

INTRODUCTION

Pre-transfusion testing had come a long way since 1901 when Karl Landsteiner discovered the first blood group. Historically, in 1945-1980, the standard for pre-transfusion testing started with detecting all possible antibodies regardless of whether it was clinically significant or not using the Coombs test [1]-[2]. They are followed by a trend from 1980 onwards, which focuses only on detecting outcomes that have a clinical impact [2].

Currently, widespread pre-transfusion testing uses the Low Ionic Strength Saline – Indirect antiglobulin test (LISS-IAT) method, which aids in detecting IgG antibodies by reducing the zeta potential between cells and incubation time of 15 minutes at 37^{o}C before proceeding to indirect Coombs test [3]. The LISS, in general, will lead to a decrease in incubation time and identify clinically significant antibodies. However, recent advances in Immunohematology challenge these pre-transfusion techniques that we are accustomed to.

Immunotherapy drugs such as Daratumumab or Anti-CD38, which are mainly used for the treatment of multiple myeloma, are also recently under clinical trials to treat other diseases. Because of the effectiveness of this immunotherapy treatment, it is increasingly used; however, the impact of Daratumumab's effect with pre-transfusion immunohematology testing was not closely studied [4]. The drug was eventually found to create false-positive results during antibody screening. Daratumumab was even found to influence pre-transfusion testing for up to six months [5]-[6]. These drugs cause pan reactive or non-specific reactions during antibody screening [7]-[8]. Specifically, these drugs attach to the CD38 portion of the cell and cause a false positive result during IAT.

In Asia, especially in Taiwan and China, the preferred standard primary reagent for pre-transfusion screening is the Polybrene method [9]-[10]. There is currently an ongoing case study about the effectiveness of the polybrene method to detect alloantibodies. The investigators have initially found that even after treatment of Daratumumab, the polybrene method still yielded accurate negative results [11]. In Qatar, the Department of Laboratory Medicine and Pathology (DLMP) of Hamad Medical Corporation is the referral laboratory for the whole State of Qatar, and it is the institution solely responsible for the blood supply in Qatar. The process of pre-transfusion testing is patterned on the Western standard of transfusion medicine. The institution is College of American

Pathologists (CAP)-accredited and continually applying for other international accreditation. Accordingly, the institution is currently utilizing LISS-IAT for pre-transfusion screening. However, this method has been confirmed to be susceptible to interference with immunotherapy drugs.

There are other methods for antibody detection in the profession. However, the ideal and best methods should be ascertained, or a combination of both should be considered to produce accurate and precise results [9] Different options have already been explored to resolve this discrepancy, but it is still subject to more investigation [12].

One of the few methods that was studied is the use of Dithiothreitol (DTT). Overcoming anti-CD38 interference through DTT was well-validated, cheap, and easy to apply; however, it correspondingly destroys the Kell antigen and other important antigens like Lutheran, JMH, LW, Cromer, Indian, Knops, and Dombrock system [13]-[14].

Another option is Trypsin and Papain, which mitigate the interference by cleaving the CD38 antigen on the reagent RBCs, but this also destroys the MNS and Duffy system [12].

Likewise, the DaraEx Reagent [15] is an anti-CD38 counteracting agent coming up short on a human Fc segment that can neutralize anti-CD38 without influencing different antigens or alloantibody response. This method was proposed and postulated as a simple, rapid, and effective method in resolving the interferences secondary to the Daratumumab monoclonal antibody without producing the same adverse effects as DTT [16]. However, this reagent is not yet widely available and is uneconomical.

Lastly, there are options such as the anti-idiotype antibody, soluble CD38 antigen, F(ab')2, and Cord blood [17], all considered effective in mitigating the interference of Daratumumab. However, these options are expensive and are not readily available for commercial use [12]-[18].

Additional testing is performed to ensure that accurate results are produced, but it can also increase the turnaround time and creates congestion for testing patient samples in the lab. These extra procedures also generate unnecessary expenditures of reagents which also increases the costs incurred by the lab.

The issues and challenges mentioned earlier compelled the researcher to find out the most effective method in conducting antibody screening for transfusion of patients taking monoclonal antibody drugs.

This present study aims to assess if the Polybrene technique can eliminate the interference caused by the immunotherapy drug during antibody pretransfusion screening on patients taking anti-CD38 in Qatar. Specifically, it seeks to compare the pre-transfusion screening results using LISS-IAT and manual polybrene techniques and determine whether there is a significant difference to the results obtained. Furthermore, suppose the polybrene method will be proven to be a more effective and precise potentiator, it will be recommended to be utilized as an alternate antibody detection process during pre-transfusion for patients taking immunotherapy drugs.

MATERIALS AND METHODS

Selection of Participants

A total of 20 patients from HAMAD hospital confirmed to be taking anti-CD38 medication were selected for the study. Following the Health Insurance Portability and Accountability Act of 1996, the privacy rule of the "minimum necessary standard," verification of the data was limited to the patients' medical and blood bank records using the hospital's Hematos and Cerner LIS.

Preparation of Samples

The plasma samples used in the study were de-identified residual patient samples obtained from the clinical laboratory of HAMAD hospital. These samples were tested using the LISS-IAT and manual polybrene techniques.

Under a laboratory setting, a different laboratory technologist tested all the samples against LISS-IAT and Polybrene technique. Again, patient identifiers were anonymous to the medical technologist.

Polybrene Kit

The LIP (low ionic Polybrene) and LIPAT (low-ionic Polybrene indirect antiglobulin tests) were performed using the reagent kit from BASO Inc. made under a worldwide quality administration framework ISO9001 and ISO13485 in a GMP-certificated manufacturing plant [19]. The kit contains the Low ionic strength medium (LIM), polybrene solution, and resuspending solution (sodium citrate-glucose solution).

LIP (Low ionic Polybrene) or Manual Polybrene Method

As previously described, the manual polybrene method [20]-[22] for antibody screening was performed using the plasma from patients taking monoclonal antibodies against the red cells from Immucor panel cells.

The procedure from Polybrene Test Kit-Blood Bank Series-Baso Diagnostic Inc. was adopted for the test. Three glass tubes labeled SI, SII & SIII were prepared. One drop of Immucor Panoscreen cells suspension was transferred in each tube. Then, 2 drops of the patient's plasma were mixed in each tube before adding 0.6 ml of LIM. The tubes were mixed well and left standing for 1 min. at room temperature. Next, two drops of 0.05% Polybrene are added, and the tubes were allowed to stand for 15 seconds.

If the specimen contains heparin, 6 more drops of 0.05% Polybrene would be added prior to centrifugation at 3400 rpm for 15 seconds, and the supernatant was decanted. Agglutination was observed. If there is no agglutination, the testing would be repeated. After which, two drops of the resuspending solution were added to each tube to neutralize the effect of the Polybrene. Lastly, gentle shaking was done to observe for agglutination within 10 seconds [19].

If Polybrene causes agglutination, it would spread out. If the agglutination is still there, the test is positive, and the antigen-antibody interaction will be graded from '0' to '4' [20]-[22]. If the results are weak, then it was examined microscopically.

LIPAT (low-ionic Polybrene indirect antiglobulin tests)

The supplemental AHG phase or Low ionic polybrene antiglobulin test (LIPAT) was done to continue the LIP method. In this process, the cells were washed three times, decanted, and 2 drops of anti-IgG serum were added. Then, the mixture was mixed for 15 seconds. After which, the reaction was read and record. If the mixture shows no agglutination, it was reported as negative. Lastly, check cells were included in the mixture to ensure that AHG was added.

If the result is still negative after including the check cells, the testing must be repeated [19].

Immucor Panoscreen three cell

Panoscreen 3 vial set by IMMUCOR was utilized for the detection of unexpected alloantibodies. Each vial comprises a 2-4 percent cell suspension of group O red blood cells from a single donor. In addition, the selected donor contains the most frequent antigens [31].

LISS-IAT Antibody Screen

Three glass tubes were provided for screening cells S1, S2, and S3. The process starts by adding two drops of plasma and 1 drop of Immucor Panoscreen cells in tubes S1, S2, and S3. After the immediate spin, the presence of agglutination was observed. Next, 2 drops of LISS were added to the tubes, and then incubated at 37^{o}C for 15 minutes. After spinning, the tubes were observed for agglutination. Cells were washed using a cell washer for three-cycle. After washing, two drops of anti-human globulin were added before mixing and centrifuging the tubes. Agglutination was read macroscopically. Check cells are added if the test is negative.

Suppose the agglutination is caused by the low ionic salt strength indirect antiglobulin test, the test would be considered positive, and the antigen-antibody interaction graded from '0' to '4' [20]-[22].

Ortho gel technique

The foil of the intended wells was removed, and the wells were labeled accordingly. In each well, 50 Ul of Surgiscreen cells were added. To each well, 40 UI plasma was delivered. Incubation at 37oC for 15 minutes, and centrifugation followed. The agglutination was graded from '0' to '4'[20]-[22].

Statistical analysis

Cochran's Q test was used to test whether there is a significant difference between the three methods. Thus, to determine where the significant difference lies, a post hoc test using Dunn's test was used. Further, statistical software, SPSS version 26, SPSS Inc., Chicago, IL, was employed to treat the data.

Ethics Approval

The protocol was submitted to the Hamad Medical Corporation Institutional Ethics Review Board (IRB) for approval prior to the conduct of the study.

RESULTS

Twenty (20) residual plasma clinical specimens from multiple myeloma patients confirmed to be taking Anti-CD38 (Daratumumab) were analyzed. Pre-screening of samples using the Ortho gel technique was performed to confirm pan-agglutination. Likewise, the Ortho gel technique verified the negative results for patients not under immunotherapy medications.

LISS-IAT results

Table 1 shows the LISS-IAT results of patients taking anti-CD38 medication. All samples were tested positive, exhibiting a weak positive reaction to 1+ in the AHG phase. No reactions were observed with the IS and 37^{o}C phases.

Table 1. LISS-IAT results from patients taking Anti-CD38 medication

Specimen	IS*	37**	AHG***	overall result
AGA 001	0	0	W+	positive
AGA 002	0	0	W+	positive
AGA 003	0	0	W+	positive
AGA 004	0	0	1+	positive
AGA 005	0	0	W+	positive
AGA 006	0	0	1+	positive
AGA 007	0	0	W+	positive
AGA 008	0	0	W+	positive
AGA 009	0	0	W+	positive
AGA 010	0	0	W+	positive
AGA 011	0	0	W+	positive
AGA 012	0	0	W+	positive
AGA 013	0	0	W+	positive
AGA 014	0	0	W+	positive
AGA 015	0	0	W+	positive
AGA 016	0	0	W+	positive
AGA 017	0	0	W+	positive
AGA 018	0	0	W+	positive
AGA 019	0	0	W+	positive
AGA 020	0	0	W+	positive

Legend *IS = Immediate Spin; **37= Incubation at 37°C; ***AHG= Anti-human Globulin

LIP method results

In Table 2, the results of the LIP methods were summarized.The twenty (20) samples tested negative with the LIP method.

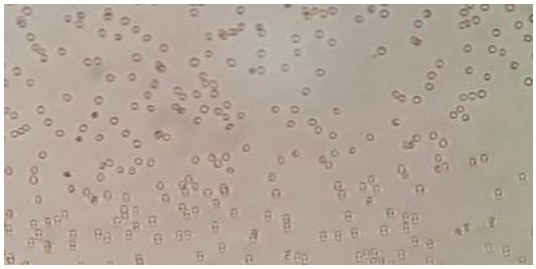

Figure 1. Image indicates no agglutination using Low ionicpolybrene (LIP) under 20X low power magnification

LIPAT results

The samples were also tested with the low-ionic Polybrene indirect antiglobulin tests (LIPAT) procedure to determine the testing accuracy for patients taking the Anti- CD38 medication. As can be gleaned in Table 3, 95% of the patients tested positive with LIPAT, either a weak or microscopically positive reaction.

Table 2 . Low Ionic Polybrene method against patients taking Anti-CD38 medication

Specimen	LIP*	overall result
AGA 001	0	negative
AGA 002	0	negative
AGA 003	0	negative
AGA 004	0	negative
AGA 005	0	negative
AGA 006	0	negative
AGA 007	0	negative
AGA 008	0	negative
AGA 009	0	negative
AGA 010	0	negative
AGA 011	0	negative
AGA 012	0	negative
AGA 013	0	negative
AGA 014	0	negative
AGA 015	0	negative
AGA 016	0	negative
AGA 017	0	negative
AGA 018	0	negative
AGA 019	0	negative
AGA 020	0	negative

Legend : *LIP=low ionic polybrene

Table 3. low-ionic Polybrene indirect antiglobulin tests (LIPAT) against patients taking Anti-CD38 medication

Specimen	LIPAT*	overall result
AGA 001	M+	positive
AGA 002	W+	positive
AGA 003	M+	positive
AGA 004	M+	positive
AGA 005	M+	positive
AGA 006	M+	positive
AGA 007	M+	positive
AGA 008	M+	positive
AGA 009	M+	positive
AGA 010	M+	positive
AGA 011	M+	positive
AGA 012	0	negative
AGA 013	M+	positive
AGA 014	M+	positive
AGA 015	M+	positive
AGA 016	M+	positive
AGA 017	M+	positive
AGA 018	M+	positive
AGA 019	M+	positive
AGA 020	M+	positive

*LIPAT= Low ionic polybrene indirect antiglobulin test

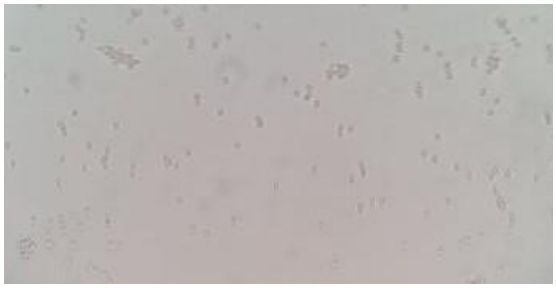

Figure 2. Image indicates the presence of agglutination using low-ionic Polybrene indirect antiglobulin tests (LIPAT) under 20X low power magnification.

Table 4
Proportions Under Different Methods

N	Cochran's Q	p-value	Interpretation
20	38.100	0.000*	Highly Significant

**Significant at α = 0.05*

To sum up, 100% of the patients tested reactive with the LISS-IAT; 100% tested negative with the LIP method; and 95% tested positive with LIPAT. Significant differences among LISS-IAT, LIP, and LIPAT were observed.

Statistical analysis using the Cochran's Q test revealed a significant difference among the three screening techniques for antibodies during pre-transfusion using the patients' residual samples at $p < 0.05$ level of significance. Based on Dunn's test, LIP emerged to be the best method.

DISCUSSION

The quantity of immunotherapy drug endorsements has been expanding, with various medicines in clinical and preclinical tests [23]. There are 2 main types of immunotherapies. The first one is Activation immunotherapy. This deals with Cancer immunotherapy, Vaccination, T-cell adoptive transfer, and Checkpoint inhibitors. The other type of immunotherapy is Suppression immunotherapy, which concerns Immunosuppressive drugs and Immune tolerance. Developments in cancer immunotherapy have come a long way since the approval and use of the first monoclonal antibody approved by the FDA, the Orthoclone OKT3® (muromonab-CD3), in 1986 [24]. And although immunotherapy is highly effective in treating cancer, this progress has proven to be a challenge when the treatment is being used in conjunction with other procedures.

Immunotherapy drugs such as Daratumumab, mainly treat multiple myeloma and recently under clinical trials to treat other diseases. However, these drugs affect pre-transfusion techniques it causes pan reactive or non-specific reactions during antibody screening [7]-[8] Specifically, these drugs attach to the CD38 portion of the cell and cause a false positive result during IAT indirect antiglobulin test.

To resolve monoclonal antibody interference in transfusion medicine, routine pre-transfusion testing has to be enhanced. The manual polybrene method used in this study test is a potentiator known to be a cheap and rapid tool for routine pre-transfusion testing. It is widely used in other Asian countries particularly Taiwan [21],[25]-[26]. This method was compared against the standard technique used in the laboratory in Qatar.

During the LISS-IAT testing, all the 20 samples were confirmed positive, with reactions ranging from weak positive to 1+, compared to the test results using the LIP method that showed complete negative results on all residual samples. This corroborates other studies that have demonstrated the superior capability of Polybrene in antibody detection when impaired by immunotherapy drug compared to manual LISS-IAT and polyethylene glycol (PEG)-IAT due to its failure to detect weakly reacting antibodies) [11],[26]-[27].

The samples we tested for the polybrene technique were done using the LIP and the LIPAT technique. The LIPAT technique differs from the LIP technique due to its additional antiglobulin phase. Between the two polybrene technique, it was clear that the LIP was more accurate as its results produced clear negative results on all residual samples. However, the LIPAT found the results demonstrating a 95% positive microscopically with occasional weak reaction. This minuscule result from LIPAT can be perceived as a mask and falsely identified as a non-specific antibody.

According to Lin and Broadberry [28], and Altaha and Jackson [26], the manual polybrene test is not widely accepted and practiced in many countries because it is not sensitive towards K antigen. It has limited sensitivity towards the Kidd blood group,[29] which is clinically significant. It was mainly used in Asia,[30] specifically in China and Taiwan, for the frequency of K antigen where it is very minimal or close to non-existent [28]. Since the samples are from Qatar, the multicultural aspect of the populace was taken into consideration, which has a varied incidence of Rh and Kell RBC antigens and performed a complementary antiglobulin test (LIPAT) on the sensitized, Polybrene-treated, red blood cells [26],[32].

It is important to note that blood transfusion is one of the most common practices performed during hospital admissions, and many transfusions are

managed with a short turnaround time. The antibody screening is an essential test wherein the patient's plasma or serum is tested against commercial reference cells with known antigen expression. A positive antibody screening indicates the presence of alloantibodies against the antigens on the commercial reference cells [33]. Therefore, it is vital that before transfusion, testing should be done with utmost care and efficiency because one mistake can cause a fatal hemolytic transfusion reaction.

The current widespread pre-transfusion antibody screening requires using the LISS-IAT method, which aids in detecting IgG antibodies by reducing the zeta potential between cells and incubation time to 15 minutes at 37c before proceeding to indirect coombs test [3]. The LISS, in general, will lead to a decrease in incubation time and identify clinically significant antibodies [2]. However, although LISS has been a standard tool used in routine pre-transfusion antibody screening, it also has its disadvantages.

The disadvantages of using LISS include increased reaction towards cold and clinically insignificant antibodies plus binding of complement becomes non-specific if ionic strength is too low [2]. Hence, this would require laboratory technologists to spend extra time identifying an antibody that is not clinically significant. Another disadvantage of LISS is the non-detection of anti-e by routine IAT and enzyme tests. The correct results for this condition can only be taken through an Auto Analyzer Polybrene (AAP) system. Low ionic strength antiglobulin methods cannot detect anti-JKA when mixed with anti-C and anti-E. This proves that LISS-IAT tests fail to detect weak reactive antibodies and eventually cause a hemolytic transfusion reaction [26].

There are other methods for antibody detection in the profession. However, the ideal and best methods should be ascertained, or a combination of both should be considered to produce accurate and precise results [9]. Different options such as the use of DTT, trypsin/papain, use of DaraEX reagent, and anti-idiotype antibody have already been explored to resolve this discrepancy. However, it is still subject to more investigation [12].

CONCLUSION

With the advent of developments in immunotherapy, combating various diseases demands adapting procedures to accommodate the evolution of methodology and to secure precise results.

As presented in this study, Anti-CD38 (Daratumumab), a drug used for immunotherapy treatments, has been proven to interfere with routine pre-transfusion screening methods. It was conclusively established that the LISS-IAT method is not reliable in testing patients taking the Anti-CD38 (Daratumumab) drug because the results using this test showed false positives. On the other hand, the LIP method has presented accurate and definitive results. While all other alternative pre-transfusion screening methods have drawbacks that are either complicated, expensive, or impractical, the LIP method offered accurate results while providing an efficient and functional process.

Additionally, the LIPAT method, a supplementary procedure for the polybrene method, is not recommended in pre-transfusion screening because it displayed weak to imperceptible positive results.

In conclusion, there was a significant difference observed among the three methods. The study demonstrated that the LIP method without the added antiglobulin phase (LIPAT) procedure is the most accurate and definitive way to conduct pretransfusion screening for patients undergoing immunotherapy.

RECOMMENDATION

It is recommended by the results of this study that if the patient is proven to be taking immunotherapy drugs such as Anti-CD38, the manual Polybrene or LIP should be the method of choice in conducting the pre-transfusion screening.

To address the issue of limited LIP sensitivity towards the K antigen and its effects, it is suggested to provide K negative units when using the LIP method. This will diminish interference without having to conduct additional antiglobulin testing.

The wide range of use for immunotherapy drugs plus the lack of understanding of its effects can lead to inaccuracies in the outcome of testings. Institutions providing pre-transfusion screenings should be aware of these immunotherapy drug interactions and adjust their procedures accordingly. We should be more conscious and responsive to the need to modify our processes to comply with the advancements in immunotherapy and provide exact and conclusive results for our patients.

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