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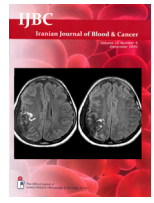

ORIGINAL ARTICLE

Prevalence and Specificity of Red Blood Cell Alloantibodies among Patients with Solid Tumors in a Teaching Hospital in Malaysia

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ABSTRACT

Background: Red blood cell (RBC) alloimmunization is an important complication following repeated packed RBC transfusions in patients with anemia. We aimed to determine the prevalence of RBC alloimmunization and the characteristics of the RBC antibodies among patients with solid tumors in Hospital Universiti Sains Malaysia (Hospital USM).

Methods: A cross-sectional study was performed from May 2018 to May 2019 in the Transfusion Medicine Unit of Hospital USM, on 322 adult patients with solid tumors. The blood samples were screened for the presence of RBC alloantibodies. Samples with positive antibody screening were subjected for antibody identification.

Results: The mean age of the patients was 52 years old. Most were Malays (91%) and female (61.2%). The three most common cancers were breast (32.3%), gastrointestinal (16.8%) and head and neck (14.0%). The overall prevalence of RBC alloimmunization was 5.3%. Most alloimmunized patients had a single alloantibody (88.2%). The anti-Mi^a comprised the most common alloantibody (26.3%) followed by anti-E (10.5%) and anti-Le^a (10.5%).

Conclusion: This study showed low prevalence of RBC alloimmunization among patients with cancers. The alloantibodies were clinically non-significant. Thus, routine antibody screening and extensive RBC phenotyping in cancer patients who need multiple transfusions is not warranted.

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Introduction

Cancer is an important public health problem in Malaysia which contributes to the third most common cause of death in the country, ranked after respiratory and circulatory system disorders.[1] Anemia occurs prevalently in patients with cancer. As a consequence, RBC transfusion has become an important modality in the management of cancer patients with symptomatic anemia.

RBC alloimmunization is one of the important undesirable events that occur as a result of repeated allogeneic blood transfusions due to the response of recipient's immune system to foreign RBC antigens.[2, 3] This can impose a major problem in the case of long-term transfusion and result in difficulties in cross matching of blood. Only a few studies have been reported on RBC alloimmunization following repeated blood transfusion in patients with malignancies. The prevalence of alloimmunization in various malignancies has been reported to be in the range of 5 to 30%[2-4] and lower in patients with solid tumors, around 1 to 11%.[2, 4, 5]

There is no study on the RBC alloimmunization in patients with solid tumors in Malaysian population.

This study was done at Hospital USM to determine the prevalence and distribution of RBC alloantibodies among cancer patients. The data might be different from previous studies in other countries as RBC antigens and alloantibodies vary among different human population and ethnicities.[6]

Materials and Methods

This is a cross-sectional study involving 322 adult patients (18 years old and above) with solid tumors who were being treated at Hospital USM from May 2018 until May 2019. Eighteen patients noted to have positive antibody screening in which one of them noted to be due to autoantibody. Ethical approval was obtained from Human Research Ethics Committee of the University (study protocol code: USM/ JEPeM/17120684).

Antibody Screening and Identification

About 3 ml of venous blood was collected in ethylene diamine tetra acetic acid (EDTA) container from each patient. Patients' blood was tested for ABO and Rh grouping. Antibody screening was performed using three-cell panel at 37°C by saline indirect antiglobulin test, using commercial screening cell reagent, ID-Diacell I- II-III Asia. Samples with positive antibody screening were analysed further with antibody identification test using another eleven-cell panels, using low ionic strength solution (LISS) and enzyme method (papain was used to treat the RBCs). The entire test was performed using commercialized cell panel by microcolumn gel agglutination method from Diamed-ID micro typing system (DiaMed-ID®; Bio-Rad Laboratories, DiaMed GmbH, Cressier FR Switzerland). Following identification of specific antibody, RBC phenotyping was performed to confirm the presence of the antibody identified.

Statistical Analysis

Data was entered and analysed using IBM SPSS version 24. The data obtained was expressed as mean and standard deviation (SD) for numerical and the categorical variables were described in frequency and percentage (%).

Results

The mean age of the patients was 52 (13-73) years and most were Malays (91.0%). More than half of the patients were females (61.2%). The three most common solid cancers were breast (32.3%) followed by gastrointestinal (16.8%) and head and neck (14.0%) cancers. Most of the patients (80.1%) had history of blood transfusion (table 1).

17 patients were detected to have alloantibody with the overall prevalence of 5.3%. Most patients developed single alloantibody (88.2%). The commonest identified alloantibody was anti-Mi^a in 5 (26.3%) followed by anti-E and anti-Le^a, each in 2 (10.5%) patients. The alloantibodies were mainly clinically not significant (table 2).

Most alloimmunized patients were female with advanced stage of the disease and positive history of blood transfusion in 14 patients. Six patients had history of RBC transfusion of more than 10 units. The details of all 17 alloimmunized patients are shown in table 3.

Table 1: Characteristic of patients with solid tumor, blood grouping and Rh, and history of transfusion (n=322)

Variables	Frequency, n	Percentage, %
Age (years)		
≤40	57	17.7
41-60	169	52.5
>60	96	29.8
Race		
Malay	293	91.0
Chinese	23	7.1
Indian	1	0.3
Others	5	1.6
Sex		
Male	125	38.8
Female	197	61.2
Type of cancer		
Breast	104	32.3
Gastrointestinal	54	16.8
Head and neck	45	14.0
Musculoskeletal	30	9.3
Gynaecological	29	9.0
Lung	20	6.2
Urogenital	24	7.4
Others	16	5.0
Stage		
Early (stage I and II)	52	16.2
Advanced (stage III and IV)	221	68.6
Unknown	49	15.2
ABO and Rh D blood group		
O RhD positive	116	36.0
A RhD positive	91	28.3
B RhD positive	95	29.5
AB RhD positive	20	6.2
History of PRBC transfusion		
Yes	258	80.1
No	64	19.9

PRBC:packed red blood cell

Discussion

RBC alloimmunization is a well-known complication following repeated allogenic RBC transfusions. Previous studies in different cohorts such as in multiple transfused patients, thalassemias, sickle cell disease, hematological disorders and solid tumor patients reported variable numbers of prevalence of RBC alloimmunization.[2, 6-9] Our study reported that the prevalence of RBC alloimmunization among cancer patients was 5.3% which was within the reported range of 1% to 11% by other studies.[2, 4, 5, 7] This range can be attributed to different factors including demography of the patients, type of malignancy, other comorbidities, type of treatment, number of transfusions, local transfusion policy and methodological and statistical heterogeneity of the studies.

Our result showed a higher rate of alloimmunization compared to another local study among patients with hematologic malignancies.[10] The lower rates observed in patients with hematological malignancies could be partially explained by impairment of the lymphocyte functions.[11]

More than half of these alloantibodies were not clinically

Table 2: Distribution of RBC alloantibodies according to the specificities and clinical significance in 17 alloimmunized cancer patients

RBC alloantibody	Frequency, n	Percentage, %	Clinical significance
Number of alloantibody			
Single	15	88.2	
Multiple (2 or more)	2	11.8	
Antibody specificity (n=19)			
Rhesus	3	15.8	
Anti-E	2	10.5	Yes
Anti-c	1	5.3	Yes
Kell	1	5.3	
Anti-K	1	5.3	Yes
Kidd	2	10.6	
Anti-Jk^{a}	1	5.3	Yes
Anti-Jk^{b}	1	5.3	Yes
Duffy	1	5.3	
Anti-Fy^{b}	1	5.3	Yes
MNS	7	36.9	
Anti-M	1	5.3	Rarely
Anti-S	1	5.3	yes
Anti-Mi^{a}	5	26.3	Rarely
Lewis	2	10.5	
Anti-Le^{a}	2	10.5	Rarely
Lutheran	1	5.3	
Anti-Lu^{a}	1	5.3	Rarely
No specificity	2	10.5	No

Table 3: Demographic characteristics of 17 alloimmunized cancer patients

Pt	Age (yrs)	Sex	Diagnosis	ABO blood group	Antibody specificity	Transfusion	Number of PRBC transfused	Pregnancy history	Stage of disease
1	54	F	Breast cancer	B	Anti-c, -Jk^{a} (b)	Yes	5	Unknown	IV
2	58	M	Gastric cancer	A	Anti-Fy^{b}, -S (a)	Yes	7	NA	IV
3	35	F	Breast cancer	B	Anti-E	No	0	Yes	IV
4	63	F	Metastatic papillary cancer	A	Anti-E	Yes	13	Yes	IV
5	54	F	Cervical cancer	A	Anti-Jk^{b}	Yes	1	Yes	IV
6	62	F	Gluteal cancer	A	Anti- K	Yes	15	Yes	IV
7	54	F	Parotid gland cancer	A	Anti-M	No	0	Yes	IV
8	30	F	Breast cancer	O	Anti-Mi^{a}	Yes	14	Unknown	Unknown
9	47	F	Ovarian cancer	A	Anti-Mi^{a}	Yes	13	Yes	III
10	69	F	Rectosigmoid cancer	B	Anti-Mi^{a}	Yes	1	Yes	Unknown
11	46	M	Malignant peripheral nerve sheath tumour	B	Anti-Mi^{a}	No	0	NA	IV
12	37	M	Scalp dermatofibrosarcoma protuberans	B	Anti-Mi^{a}	Yes	3	NA	IV
13	54	F	Thyroid cancer	A	Anti-Le^{a}	Yes	1	Yes	IV
14	43	M	Lung cancer	O	Anti-Le^{a}	Yes	26	NA	IV
15	53	M	Bladder cancer	A	Anti-Lu^{a}	Yes	4	NA	IV
16	59	F	Endometrial cancer	O	Antibody with no specificity	Yes	3	Yes	IV
17	52	F	Breast cancer	A	Antibody with no specificity	Yes	28	Yes	IV

yrs: years; F: Female; M: Male; a: The first and second alloantibodies were detected simultaneously; b: The second alloantibody was detected 6 weeks after the first alloantibody; PRBC: Packed red cell; NA: Not applicable

significant including anti- Mi^a, anti-Le^a, anti-Lu^a and antibodies with no specificities.

The commonest alloantibodies in our study were anti-Mi^a followed by anti-E and anti-Le^a. Previous studies in western populations have reported different alloantibodies among cancer patients including anti-E, anti-Fy^a, anti-Fy^b, anti-Jk^a, anti-K, anti-C and anti-e.[2, 12] It is reported that anti-Mi^a antibody is common in South East Asian populations, but very rare in Caucasians. Anti- Mi^a antibody has been described as the most common alloantibody in several studies in non-malignant transfusion recipients of Asian populations.[8, 13, 14]

Anti-E has also been reported to be the commonest alloantibody in hematologic and non-hematologic patients.[2, 4, 10, 15] There are several explanations for these findings: 1) it shows that E antigen is highly immunogenic and individuals who are E-antigen negative are susceptible to develop anti-E alloantibody if exposed to E-antigen positive RBCs,[16] 2) Among Malay population, E-antigen negative individuals are common accounting for about 77% of population in which R1R1 (CDe/CDe), R1r (CDe/cde) and rr (cde/cde) account for 61.5%, 15% and 0.5%, respectively,[17] and 3) Anti-E can also be a naturally occurring antibody.[18]

Our data showed that the majority of alloimmunized patients have a single rather than multiple alloantibodies. In our study, only two patients developed multiple alloantibodies. The first patient had anti-c which subsequently developed anti-Jk^a. The second patient had anti-Fy^b and anti-S detected simultaneously. In RBC alloimmunized patients, it has been reported that the probability to develop additional antibody would be increased by 3.3-fold.[4] Thus, in repeatedly transfused patients, we need to be aware of the risk of developing multiple antibodies in the course of time. Because of this finding, many authors have advocated the use of extended phenotypic matching of packed RBCs for repeatedly transfused patients. We are unable to predict the most prevalent antibody combination as only a small number of patients have more than one antibody.

A limitation of our study was that antibody screening method may not detect antibody towards low incidence antigens or very low antibody titres. Thus, we might underestimate the true prevalence of RBC immunization among patients with solid tumors.

Conclusion

The prevalence of RBC immunization was relatively low among patients with cancer treated in our centre. In addition, most of the RBC antibodies identified were not clinically significant. Our study justifies the current practice in our center in which only patients who already developed clinically significant alloantibodies to be issued antigen negative RBCs. In addition, routine antibody screening may not be indicated in all patients with solid tumors, but may only be performed in patients with incompatible cross match which indicates the presence of clinically significant alloantibodies in their plasma.

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Conflict of Interest: None declared

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