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Review Article

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Blood Transfusion in Patients with Immunohaematological Problem

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Abstract

The blood transfusion therapy is an essential in the management of hematologic/ oncologic disorders. Although transfusions are not risk free. In fact, this patient may develop alloimmune or autoimmune process during the transfusion support. Alloimmunization is a significant risk of transfusions and is the second leading cause of transfusion-associated death. In fact, the transfused individuals with hematologic/oncologic disorders may develop red blood cell alloantibodies, which can complicate pretransfusion testing, delay blood product availability, and lead to transfusion reactions. The autoimmune haemolytic anaemia may be produced by cold and warm autoantibodies and may mediate intravascular or extravascular autoimmune haemolysis in haematology/oncology patients. Many immunohematology tests performed by blood banks, including antibody screening, direct antiglobulin tests, eluates, and minor antigen phenotyping, are used in the assessment of haematology/oncology patients who require transfusion care, or in whom an alloimmune or autoimmune process is suspected. The tests that form the basis for transfusion compatibility and antibody identification are not always well understood, nor are their interpretations always straightforward. A better understanding of testing realized in the immunohematology laboratory will allow haematology/oncology providers to make informed decisions on the risk/benefit ratio of transfusion for their individual patients. Further, this understanding will allow improved communication between haematology/oncology providers and the transfusion Service in instances of transfusion histories, new antibody formation, and unexpected adverse transfusion sequelae.

Keywords: Blood Transfusion, Autoimmune Haemolytic Anaemia, Autoantibodies, Antiglobulin test

Introduction

Cancer patients often have hematological disorders, and can affect erythrocytes, platelets, leukocytes or blood proteins [1]. Of these alterations, anemia is the most frequent (50% of oncological patients will have it at some point in their illness). Being their highest frequency in patients with hematologic neoplasms (30-40% in lymphomas; 70% in myeloma and myelodysplastic syndromes [2].

The cause of anemia is often multifactorial, and can be caused by nutritional disorders, hemorrhage, autoimmune hemolysis, erythroid aplasia, chronic disorders, or chemotherapy and radiotherapy [3].

Therefore, transfusion therapy is essential in the treatment of hematological/oncological disorders.

In effect, transfusions improve symptoms very quickly; However, some complications may appear, mostly mild, and some serious, but they can lead to death [4,5]. In this brief review, we discourse the immunohematological problems that could occur in oncologic patients and how to interpret the laboratory results for the best decision making.

Transfusion risk

Without a doubt, blood transfusion has never been as safe as it is now, however, there is a belief in the medical community that it is a simple and safe procedure [6]. Transfusion is a tissue graft (the most common of medical practice) and, like all medical intervention, involves risks inherent to the procedure and the biological origin of the component. Blood transfusion is not riskfree [7].

Indeed, the prevalence of adverse reactions is:

1. Mild: 1:100
2. Serious: 1:370
3. Fatal 1:117.000

Compared to other medical practices, for example: The risk of death by medical error is 1:1,000 by anesthesia 1:185.000 and obstetric cause is 1:7.653 [8-11].

Analysis of this data also arises that administrative errors are an important category of reactions; being the bedside of the patient is the weakest link that involves the health system [12].

Many reactions are inevitable, the immune cause is 1.000 a 10,000 greater than the risk of transfusion transmissible infections [13].

Indeed, even oncologic patients can develop alloimmune or autoimmune processes during the transfusion support of their treatments. Alloimmunization is a significant risk of transfusions and is the second leading cause of transfusion associated death.

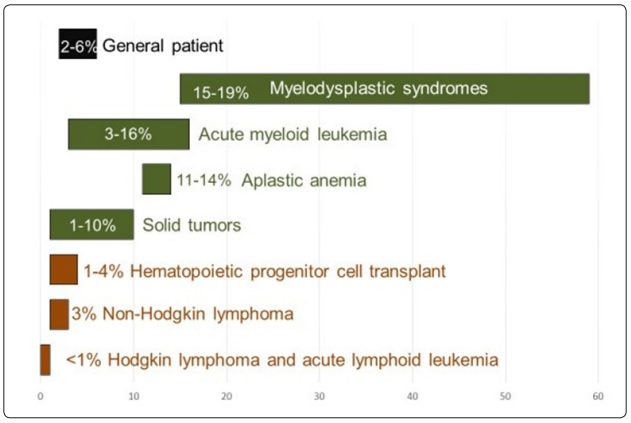
Alloimmunization

Usually oncologic patients are transfused by selecting compatible ABO and RhD components, without taking in account other antigens present in the human blood (polymorphism) being able to develop alloantibodies against antigens present in the transfused component ang that patients do not. These alloantibodies may be responsible for:

1. Complicate pretransfusion compatibility tests,
2. Delaying the availability of blood products
3. Cause transfusion reactions.

Despite the high degree of immunosuppression (both by the basic disease itself and the drugs used in its treatment), oncologic patients can still mount an immune response to erythrocyte antigens, platelets or leukocyte Foreign.

The degree of alloimmunization to red blood cells (RBC) antigens in general patients is 2% to 6% [14]. Instead, those patients with a dysfunctional immune system are hyper or hyposensitive can result in increased or decreased antibody production. The patients with myelodysplastic syndrome may present different degrees of sensitization between 15 to 59%; Acute myeloid leukemia 3% to 16%; aplastic anemia 11-14% and patients with solid tumors 1% to 10%. On the other hand, patients with lymphoid leukemia and Hodgkin lymphomas (< 1%), Non Hodgkin's lymphomas, transplanted with hematopoietic progenitors (1%-4%) show a significant decrease in the alloimmune response to erythrocytes, probably related to the own disease or intense immunosuppressive therapy; It still does not prevent the immune response from RBC antigens [15]. (Graphic 1)



Graphic 1: Prevalence of RBC alloantibodies in oncology patients

Autoimmune Hemolytic Anemia

Hospitalized patients may present RBC autoantibodies between 7-8% of them; The range of pathogenicity is widely variable, from the clearly benign (without apparent hemolysis) to the fatal hemolysis [16,17].

Hemolysis is a decrease in the half life of circulating RBC. When the immune system is involved, an autoimmune hemolytic anemia (AIHA) appear. In the patient there are clones of B lymphocytes producing autoantibodies (AuAb) anti RBC autoregulated (apoptosis, anergic or suppression by lymphocytes T_{Reg}) When these regulatory mechanisms fail, AuAb are produced in enough quantity and quality to destroy the self RBC [18]. Molecular mimicry, dysfunction T-B, polyclonal activation B, escape to thymic deletion or even emergency of RBC lacking CD55, CD59) (Figure 1).

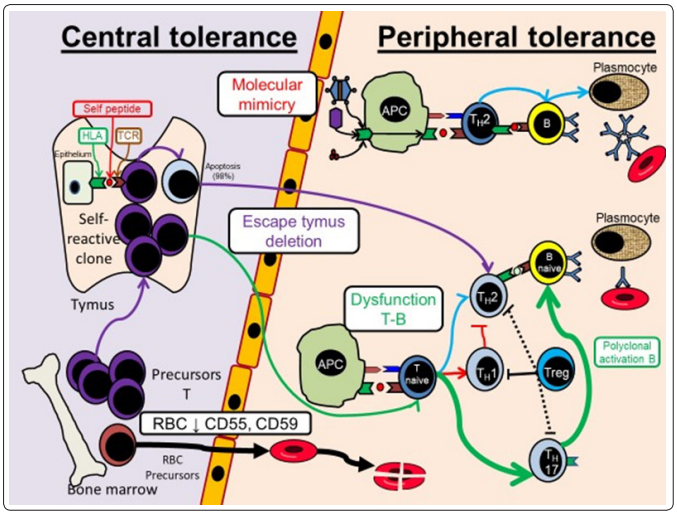


Figure 1: Escape mechanisms to immune tolerance in autoimmune hemolytic anemia
APC: Antigen presenting cells
TCR: T Cellular Receptor
RBC: Red cells

AIHA is characterized by the presence on the RBC surface of AuAb and/or fractions of the complement (C3d); the detection (by Coombs ' test) and demonstration of clinically significant hemolysis constitutes the spine of its diagnosis [19].

AIHA can be produced by cold (IgM) and/or warm (IgG) AuAb and may mediate intravascular or extravascular hemolysis in hematologic/oncological patients (Figure 2).

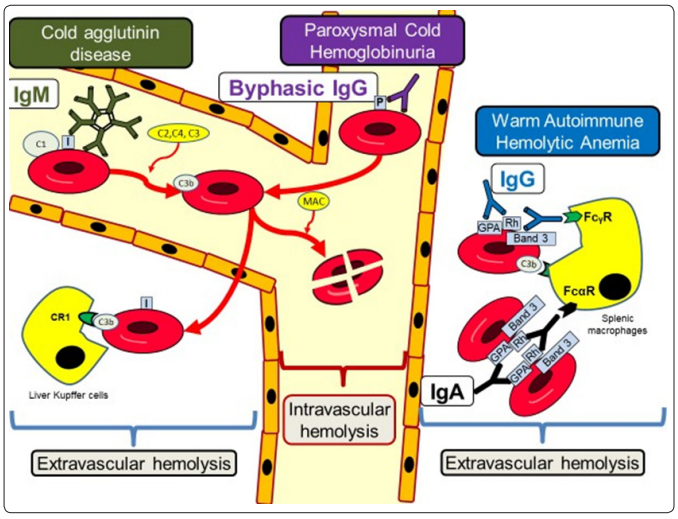


Figure 2: Mechanisms of immune hemolysis
CR1: Complement Receptor 1
MAC: Membrane attack complex

Some AIHA may be secondary to other diseases (infections, neoplasms, systemic diseases), being hemolysis the onset or the only clinical expression. In other cases, there is no underlying disease and are idiopathic AIHA.

In a patient with clinical hemolysis and recent transfusion history (last 3 months) the most important differential diagnosis is the pos transfusion hemolytic reaction [20,21].

Immunohematological Diagnosis

Many immunohematological tests performed by blood banks, including antibody analysis, direct Antiglobulin tests, eluted and phenotyping of minor antigens, are used in the assessment of hematologic/oncological patients who require transfusion care or in whom alloimmune or autoimmune process is suspected.

Direct Antiglobulin (Coombs) Test (DAT)

The DAT is the most important technique in the study of a patient suspected of AIHA. If the DAT is positive, the use of anti IgG and anti-C3D allows its classification in IgG alone (warm AIHA), C3d alone (cold) or both IgG and C3d (warm AIHA, or mixed AIHA) [22,23].

This classification has an excellent clinical correlate, since in AIHA (IgG) hemolysis is extravascular, while in cold AIHA is intravascular by the activation of the complement. Between 2-10% of the warm AIHAs course with negative DAT, this requires using techniques which and quantitatively different from the conventional DAT [24] (Table 1).

Table 1: Classification of AIHA

			Antiglobulin test		Elution
			Direct	Indirect	
Warm AIHA		IgG	IgG/C3	IgG	IgG
Cold AIHA	Cold Aglutinin disease	IgM	C3	30º C Alb	Neg
	Paroxysmal cold hemoglobinuria	IgG	C3	Neg (D-L +)	Neg
Mixed AIHA		IgG+IgM	IgG/C3	IgG+IgM	IgG
Drug-induced IHA	Drug-Independent	IgG	IgG	IgG	IgG
	Drug-Dependent	IgG	IgG/C3	Neg	Neg
		IgM	C3	Neg	Neg

D-L: Donath-Lansdteiner Test

Elution

It is used to confirm the presence of AuAb (AIHA DAT negative, Drug Induced AIHA) and the diagnosis of post transfusion hemolytic reaction [20,21].

Indirect Antiglobulin (Coombs) Test

The patient's serum should be studied for:

1. Alloantibody detection; Only clinically significant matters
2. Diagnosis of cold agglutinins
3. Donath-Landsteiner (DL) test for PCH suspicion

Warm Autoimmune Hemolytic Anemia

They represent 70% of the AIHA [17]. 73.5% of AIHAC are secondary to other diseases (leukemias, lymphomas, lupus) and 26.5% idiopathic [23-27].

At the time of presentation, it is mostly insidious (87.5%) and the acute forms form only 12.5%, jaundice occurs in about 40% of patients, adenopathy in 25%. In the most severe cases hemolysis is intense, the anemia is acute, and it is established quickly.

The DAT is positive by anti IgG and/or C3. Haptoglobin is significantly decreased or undetectable in 70%. Some cases of AIHA are accompanied by immune thrombocytopenia, in which case it constitutes Evans syndrome.

The initial treatment consists of corticotherapy. The response occurs in the first week and forwards 80-90% of idiopathic AIHA and 50% secondary.

Before the failure of corticotherapy and/or splenectomy may be useful other immuno suppressants, such as azathioprine, cyclophosphamide or Rituximab [28,29].

Cold Autoimmune Hemolytic Anemia

They constitute 30% of the AIHA, there is by two types: Cold Agglutinin Disease (CAD) and Paroxysmal Cold Haemoglobinuria (PCH) [17].

In CAD, the AuAb are mostly IgM and pathogenicity depend on their ability to activate complement (intravascular hemolysis); The surviving RBC are eliminated from the circulation, mainly by the macrophages of the liver.

The increase in the degree and thermal amplitude of the AuAb may be by infections by *Mycoplasma pneumoniae*, infectious mononucleosis and other viruses; Sometimes with Leukemia or other lymphoid neoplasms. The secondary cases to infections may be in the form of acute hemolysis, which occurs at 5-10 days after the end of the infection and usually remitting spontaneously.

In idiopathic cases or associated with lymphoproliferative processes it is manifested as a chronic anemia.

Usually presents DAT Positive by anti C3 (negative with anti IgG) a reactive AuAb at 30 ºC.

Cases of acute (secondary) hemolysis, although severe, are self limiting and most of them recover spontaneously.

The treatment is to keep the patient in a warm environment, avoiding exposure to cold and as the first line of treatment rituximab with or without fludarabine avoiding the use of corticosteroids [29-31].

In the PCH, the present AuAb is IgG Biphasic Hemolysin (Donath-Landsteiner), as it sensitizes the RBC in cold, but only hemolyze it is reached 37º C. It is presented in young males with the antecedent of a viral infection; After exposure to cold, a picture of chills, fever, lumbar pain, headache, and general malaise begins abruptly. It is accompanied by hemoglobinuria. The DAT is positive anti C3d. The diagnostic test is the test of Donath-Landsteiner (DL).

The treatment is avoiding the cold eculizumab [33].

Drug Induced Haemolytic Anemia

It is a type of secondary AIHA constituted by at least two types of anti drug antibodies: Drug-independent antibodies are IgG which do not require of the drug to detect and may perpetuate hemolysis even after discontinuing the therapy with the drug. This type of antibody

is indistinguishable from warm AIHA [33,34].

Drug dependent antibodies requiring the drug to be detected in laboratory tests; That may be non binding complement IgG, clinically mild, and even subclinical or IgG and/or IgM complement activators capable of producing intravascular hemolysis can cause kidney failure or even death.

In some cases, only one of the mechanisms is predominant, however, the combinations between them have been described [35-37].

The primary resolution consists of discontinuer the drug administration, although laboratory studies have not yet confirmed it and therapeutic support with RBC transfusion and corticotherapy, with or without IVIG if the patient's condition is unstable.

Pretransfusion compatibility

The pretransfusion compatibility is a process that involves selecting RBC concentrates that have an acceptable post transfusion life. It involves carrying out the following procedures before the transfusion:

1. In the patient:

1. Verify the identity of the receiver and its blood sample.
2. ABO and RhD typing.
3. Detection and identification of irregular antibodies.
4. Comparison with previous records

2. In the RBC component:

1. ABO and RhD Retyping.
2. Selection of the appropriate components.

3. Cross Match:

1. Patient Serum vs. erythrocytes of the selected blood unit
2. Electronic cross match

4. Labeled Components:

The most critical aspects of transfusion receptors are: patient/sample identity verification; The administration of the component, its monitoring and evaluation.

There is frequent suspicion in transfusing patients with immunohematological problems, even in those with severe anemia.

Indeed, transfusion should never be considered as contraindicated, even if compatibility tests are strongly positive.

Conclusion

The tests that form the basis for transfusion compatibility and antibody identification are not always well understood, nor are their interpretations always straightforward. A better understanding of testing realized in the immunohematology laboratory will allow haematology/oncology providers to make informed decisions on the risk/benefit ratio of transfusion for their individual patients. Further, this understanding will allow improved communication between haematology/oncology providers and the transfusion Service in instances of transfusion histories, new antibody formation, and unexpected adverse transfusion sequelae.

Conflict of interests

I declare no conflict of interest, real or potential, with the content of the publication.

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