Haematology and Blood Transfusion Vol. 29
Modern Trends in Human Leukemia VI
Edited by Neth, Gallo, Greaves, Janka

Red Cell Transfusions for Polytransfused Patients

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Patients with chronic anemia tolerate much lower levels of hemoglobin than those experiencing acute blood loss or acute hemolysis. The compensating mechanism is the increase of red cell 2,3-diphosphoglycerate (DPG), causing increased release of oxygen to the tissues. For this and further clinical and epidemiologic reasons, it is unnecessary to transfuse patients with chronic anemia unless symptoms of anoxia are expressed. This rarely occurs at hemoglobin levels higher than 8 g/dl. Many patients tolerate lower levels of hemoglobin and, therefore, do not require RBC transfusions.

In leukemia, lymphoma, and iatrogenically induced anemia, there is decreased or absent production of erythrocytes. Such patients will respond well to transfusion of red blood cells (RBC) as long as increased organ-specific or peripheral destruction of erythrocytes does not occur. However, current RBC preparations also contain leukocytes and platelets. The nonerythrocytic cells possess alloimmunogenic specific antigens different from known blood groups. Thus, substitution of chronic anemia patients with RBC preparations may result in sensitization to leukocyte- and/or platelet-specific antigens [1–5]. Patients previously sensitized to leukocytes and platelets are subject to febrile nonhemolytic transfusion reactions and may be resistant to a later required leukocyte and/or platelet transfusion [6–8]. This is a further reason why transfusion of patients with chronic anemia should be restricted to absolute clinical necessity.

If red cells are needed, HLA-compatible blood is the best solution. Owing to the extreme polymorphism of the HLA system, however, this is seldom practicable. Since the occurrence of leukocyte and platelet antibodies is correlated to frequency and volume of whole blood transfusion [5, 9–11], only leukocyte- and platelet-depleted erythrocytes should be transfused.

Packed RBC are partially plasma depleted and contain 100% of the original leukocytes and platelets. The sensitizing capacity of these preparations is similar to whole blood units. But even buffy-coat-free or washed RBC preparations demonstrate the same alloimmunization pattern as whole blood, although they contain only 41% of original leukocytes and 11% of platelets (Tables 1, 2). The transfusion reaction incidence using these preparations is lower than in whole blood transfusion, but it remains impossible to predict the clinical outcome in individual patients.

I have analyzed published [12–17] and my own data [5] and calculated the minimal leukocyte alloimmunogenic leukocyte dose: 10×10^8 leukocytes transfused in 1 day (whole blood, washed buffy-coat-free RBC) or small cumulating quantities, independent of transfusion frequency and interval or donor, will cause sensitization to leukocyte antigens (Table 3; [5, 12–17]). Only leukocyte- and platelet-free preparations [5, 18–21] contain less than 4% of

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Table 1. RBC-enriched blood units

	RBC Preparation[a]	*N*	Leukocytes $\times 10^8$		Platelets $\times 10^{10}$		Hemoglobin (gramm)	
			Initial	After Preparation	Initial	After preparation	Initial	After preparation
1	Buffy-coat-free	50	25.1	10.2 (41%)	10.7	1.2 (12%)	62	50 (81%)
2	Washed	30	23.0	9.0 (42%)	9.0	1.0 (11%)	64	51 (80%)
3	Filtered	30	24.0	0.9 (4%)	10.2	0.2 (2%)	63	51 (81%)
4	Incubated (37 °C), followed by buffy-coat-free preparation	30	27.3	1.0 (3.6%)	13.2	0.03 (0.3%)	77	60 (78%)
5	Frozen	30	28.0	0.5 (2%)	11.0	0.15 (1%)	72	56 (78%)

[a] Techniques: 1, 2 leukocyte- and platelet-poor blood; 3–5 leukocyte- and platelet-free blood

Table 2. Alloimmunization patterns

	Units per patient	Patients	Alloimmunized patients	Alloimmunization rate (%)
Whole blood	16± 6 (2–34)	27	17	63
Washed RBC	14± 7 (2–68)	60	32	53
Filtered RBC	22± 9 (2–76)	44	2	4

Table 3. Alloimmunization to leukocyte antigens in RBC transfusion[a]

First immunized recipient after:	Leukocytes	Ref.
1 One whole blood unit (400–500 ml)	25×10^8	[13], [14]
2 Repeating transfusion of 80–100 ml whole blood from the same donor, after 5 weekly transfusions ($5 \times 80–100 = 400–500$ ml)	25×10^8	[22], [16]
3 As in 2, but 20 ml weekly after 9 weekly transfusions ($9 \times 20 = 180$ ml)	10×10^8	[17]
4 One unit washed buffy-coat-free RBC	10×10^8	[12]
5 Filtered leukocyte-free RBC; after 13 transfusions from different donors with clinically dependent intervals	13×10^8	[5]

[a] Conclusion: Minimal leukocyte immunizing dose = $10 \times 10^8 = 1$ unit

the initial value (Table 1); they contain fewer leukocytes than the minimal immunogenic dose (Table 4). These preparations contain only 0.1 dose compared with 1.0 in buffy-coat-free blood and washed RBC, and 2.5 doses in whole blood and packed RBC. This explains why these preparations very seldom sensitize to leukocyte antigens (Table 2); [5, 12]).

Brittingham and Chaplin [15, 22] and Perkins et al. [23] described the minimal leukocyte dose causing nonhemolytic trans-

Table 4. RBC-containing blood units

	Leukocytes $\times 10^8$ (% of initial)	Minimal leukocyte immunizing dose (10×10^8 leukocytes = 1 unit)	Leukocyte dose causing transfusion reaction (2.5×10^8 leukocytes = 1 unit)
1 Whole blood	25 (100%)	2.5	10 Leukocyte-rich
2 warm blood	25 (100%)	2.5	10 Leukocyte-rich
3 Packed RBC	25 (100%)	2.5	10 Leukocyte-rich
4 Buffy-coat-free	10 (41%)	1.0	4 Leukocyte-poor
5 Washed buffy-coat-free	10 (42%)	1.0	4 Leukocyte-poor
6 Filtered	0.9 (4%)	0.1	0.4 Leukocyte-free
7 Incubated	1.0 (4%)	0.1	0.4 Leukocyte-free
8 Frozen	0.5 (2%)	0.05	0.2 Leukocyte-free

Table 5. Recommendation for administration of RBC-containing blood units[a]

	Content (%)				Alloimmunization to leukocyte and platelet antigens	Transfusion reaction to leukocytes and platelets	Indication
	RBC	Leukocytes	Platelets	Plasma			
Whole blood	100	100	100	100	++++	++++	None!
Warm blood (<6 h)	100	100	100	100	++++	++++	1 Acute life-threatening blood loss 2 Bleeding not manageable with clotting factors and platelets 3 Massive transfusion
Packed RBC	100	100	10	30	++++	++++	None!
Buffy-coat-free RBC	81	41	12	15	++++	++	Acute life-threatening anemia without presensitization to leukocyte and platelet antigens
Washed RBC	80	41	11	0	++++	++	Hyperkalemia, allergic reaction, IGA deficiency
Leukocyte- and platelet-free blood							
Filtered	81	4	2	10	(+)	0	Transfusion-dependent chronic anemia: prevention of alloimmunization and transfusion reaction to nonerythrocytic blood cells
Incubated	78	3.6	0.3	20	(+)	0	
Frozen	78	2	1	0	(+)	0	

++++ Very often; ++ sometimes – often; (+) seldom = cumulating doses due to polytransfusion

fusion reaction (2.5×10^8 leukocytes). Whole blood and packed RBC contain 10 such doses, buffy-coat-free and washed RBC 4 doses, and leukocyte-free preparations only 0.2–0.4 dose (Tables 1, 4). Consequently, nonhemolytic transfusion reactions to leukocyte antigens have not been described with leukocyte- and platelet-free RBC units [5, 21].

These data indicate that only leukocyte- and platelet-free RBC minimize sensitization to leukocyte and platelet antigens, avoid nonhemolytic febrile transfusion reactions to nonerythrocytic cells of the donor, and may guarantee an efficient granulocyte and platelet substitution in RBC polytransfused patients. Recommendations for administration of RBC preparations are summarized in Table 5.

Patients with severe aplastic anemia transfused prior to bone marrow transplantation reject allogeneic grafts more frequently than untransfused patients. The mechanism for this reaction is unknown. It should be stressed, however, that even leukocyte- and platelet-free RBC contribute to graft rejection. Thus, patients with severe aplastic anemia should not be transfused prior to bone marrow transplantation. The low number of lymphocytes in leukocyte-free RBC preparations is able to cause graft-versus-host reactions. Consequently, these preparations should be irradiated before transfusion to immunodeficient patients, e.g., patients with Hodgkin's disease, patients conditioned for bone marrow transplantation, and patients with severe combined immunodeficiency.

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