Published in final edited form as:

Leuk Res. 2011 January ; 35(1): 8–11. doi:10.1016/j.leukres.2010.07.015.

What are RBC-transfusion-dependence and -independence?

R.P. Gale[*],
Imperial College London, Section of Haematology, Division of Experimental Medicine, Department of Medicine, London, UK

G. Barosi,
University of Pavia Medical School, RCCS Policlinico S. Matteo Foundation, Pavia, Italy

T. Barbui,
Hematology Division, Ospedali Riuniti, Bergamo, Italy

F. Cervantes,
Hospital Clinica, Barcelona, Spain

K. Dohner,
Department of Internal Medicine III, University of Ulm, Ulm, Germany

B. Dupriez,
Service Hématologie Clinique, Centre Hospitalier, Lens, France

V. Gupta,
Department of Medicine, Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada

C. Harrison,
Department of Haematology Guy's and St Thomas' NHS Foundation Trust Great Maze Pond, London, UK

R. Hoffman,
Mount Sinai School of Medicine, New York, NY, USA

J.-J. Kiladjian,
Hopitaux de Paris, Hôpital Saint-Louis, Centre d'investigations Cliniques (CIC 9504); and Université Paris 7, Paris, France

R. Mesa,
Mayo Clinic, Scottsdale, AZ, USA

M.F. Me Mullin,
Centre for Cancer Research and Cell Biology, Queen's University, Belfast, Ireland

F. Passamonti,

[*]Corresponding author. Tel.: +44 908 656 0484, fax: +44 908 673 2773. robertpetergale@aol.com (R.P. Gale).

Contributions. JMB,JB,TF and CLB kindly reviewed the typescript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.leukres.2010.07.015.

Conflict of interest statement

None to declare and Robert Peter Gale, M.D., Ph.D. is an employee of Celgene Corporation, Summit, NJ.

Department of Hematology, University of Pavia, Pavia, Italy

V. Ribrag,
Department of Medicine, Institute Gustave Roussy, Villejuif, France

G. Roboz,
Weil Medical College of Cornell University, New York, NY, USA

G. Saglio,
Dept of Clinical and Biological Sciences, University of Turin, Turin, Italy

A. Vannucchi,
University of Florence, Florence, Italy

S. Verstovsek
Department of Hematology/Oncology, MD Anderson Cancer Center, Houston, TX, USA

Abstract

The term RBC-transfusion-dependence is widely-used by hematologists to describe a condition of severe anemia typically arising when erythropoiesis is reduced such that a person continuously requires ≥ 1 RBC-transfusions over a specified interval. Defining a person as RBC-transfusion-dependent has important implications in diverse hematological disorders especially because it strongly-correlated with decreased survival. Conversely, becoming RBC-transfusion-independent or receiving fewer RBC-transfusions over a specified interval is defined as improvement or response in many disease- and/or therapy-setting. Whether this correlates with improved survival is controversial. We used a structured expert-panel consensus panel process to define RBC-transfusion-dependence and -independence or improvement. We suggest these definitions may prove useful to persons studying or treating these diseases.

Keywords

Anemia; RBC-transfusions; Myelodysplastic syndrome; Myeloproliferative neoplasm; Aplastic anemia; Paroxysmal nocturnal hemoglobinuria; Anemia therapy

1. Introduction

The term: “RBC-transfusion-dependence” is widely-used by hematologists to describe a condition of severe anemia typically arising when erythropoiesis is reduced or inadequate such that a person continuously requires ≥1U RBC-transfusions over a specified interval. Defining a person as RBC-transfusion-dependent has important implications in several hematological disorders including myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPNs) aplastic anemia and paroxysmal nocturnal hemoglobinuria (PNH). In these diseases RBC-transfusion-dependence is strongly-correlated with decreased survival. Conversely, becoming RBC-transfusion-independent or receiving fewer RBC-transfusions over a specified interval is defined as improvement or response depending on whether therapy is given. Whether improvement or response, so defined, correlates with improved survival is controversial.

For example, in some retrospective analyses of observational databases of persons with MDS receiving erythropoietin there is a correlation between decreased RBC-transfusions and improved survival [1,2]. However, in one study this correlation was seen only in persons receiving few RBC-transfusions. No survival benefit was found in another study [3]. This controversy resembles controversy regarding use of erythropoietin to decrease RBC-transfusions in persons with blood diseases, cancer and end-stage kidney disease where no survival benefit or even poorer survival is reported in most analyses [4,5].

Given the importance of RBC-transfusion-dependence in determining prognosis and defining therapy-response in these diseases, it is surprising there are no widely-agreed on definitions. For example, the WHO classification-based prognostic scoring system (WPSS) for MDS defines RBC-transfusion-dependence as receiving ≥1U RBC ≤8 weeks averaged over 4 months (no baseline hemoglobin level to qualify a RBC-transfusion is defined) [6]. Here, RBC-transfusion-dependence is correlated with an adjusted hazard ration (HR) for death of 2.53 (95% Cl: 1.71 to 3.75). It is unclear how this definition of RBC-transfusion-dependence was derived or whether other definitions were tested.

In contrast: the International Working Group (IWG) in MDS in 2000 proposed different criteria for RBC-transfusion-dependence: ≥1 RBC-transfusion for a hemoglobin level ≤90g/l with no surveillance interval specified [7]. In a re-analysis of a series of studies of 5-azacytidine in MDS sponsored by Cancer and Leukemia Group B (CALGB) used for FDA-approval, RBC-transfusion-dependence was defined as ≥1 RBC-transfusion within 90 days pre-study [8]. A recent study of 5-azacytidine defined RBC-transfusion-dependence as “requiring” ≥1 RBC-transfusion within 28 days of study-entry [9]. Another recent study in low-risk MDS used a definition of RBC-transfusion-dependence of ≥2U RBC every month: a significant correlation with survival was reported [10].

In contrast to these definitions of RBC-transfusion-dependence in persons with MDS, the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) consensus criteria for RBC-transfusion-dependence in persons with MPN-associated myelofibrosis (fibrotic primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF) and post-essential thrombocythemia myelofibrosis - post-ET MF) is receiving ≥2U RBC for 28 days for a hemoglobin <85 g/1 [11]. In a recent study in MPN-associated myelofibrosis, RBC-transfusion-dependence at ≤1 year of diagnosis correlated with worse survival independent of IWG prognostic staging [12]. No precise definition of RBC-transfusion-dependence was given.

These correlations between RBC-transfusion-dependence, however defined, and survival in MPN-associated myelofibrosis, for example, undoubtedly reflect the strong correlation between hemoglobin level and survival in these diseases [13–15]. However, there are two confounders in interpreting these data: (1) physicians differ considerably in the hemoglobin level they consider appropriate to trigger RBC-transfusions between diseases and between persons with the same disease (often depending on comorbidities; see below); and (2) it is difficult to know what baseline hemoglobin value to assign persons receiving RBC-transfusions, especially when different hemoglobin trigger levels operate.

The situation is equally complex and confusing in aplastic anemia where there are substantial data that increased RBC-transfusion-dependence correlates with worse survival and therapy-outcome (for example, after allogenic blood cells or bone marrow transplants) but where there is no uniform definition of RBC-transfusion-dependence.

Another example of this complexity is in trials of therapy-interventions. For example, in a recent trial of the iron-chelating drug deferasirox in persons with RBC-transfusion-dependent anemia (MDS, Blackfan-Diamond syndrome and beta-thalassemia), RBC-transfusion-dependence was defined as ≥8U RBC per year [16]. It is unclear why this number was chosen. Also, in 2 recent trials of eculizumab in PNH, different definitions of RBC-transfusion-dependence were used: 1 trial specified ≥1U RBC over 2 years where another specified ≥4 U RBC over the preceding 1 year [17–19].

There is similar variability in defining improvement in RBC-transfusion-dependence. For example, in the revised IWG MDS criteria a ≥4U decrease in RBC-transfusion frequency (given for a hemoglobin level ≤90g/l) over 8 weeks compared to a baseline 8 week interval pre-therapy is scored as hematologic improvement (major) [7]. The scientific bases for this threshold or details of the process by which it was determined are not reported. In a recent iteration of these criteria, a 50% reduction in RBC-transfusions from baseline along with a ≥20g/l increase in hemoglobin level from “baseline” is proposed as hematological improvement [20]. However, there is controversy as to how to define a “baseline” hemoglobin value in subjects receiving RBC-transfusions. In a Cancer and Leukemia Group-B (CALGB) re-analysis using the 2000 IWG guidelines RBC-transfusion-independence was defined as no RBC-transfusions for ≥56 days [8].

In contrast to these variable criteria for improvement or response in MDS, clinical improvement in the MPN-associated myelofibrosis IWG-MRT criteria is defined as becoming RBC-transfusion-independent for ≥56 days in subjects with baseline hemoglobin level <100 g/1 [11]. No benefit is ascribed to a decreased frequency of RBC-transfusions. There is no widely-accepted definition for RBC-transfusion response in persons with aplastic anemia or in other therapy-related settings in these and other diseases. Evaluation of response is equally complex in PNH where response was defined by hemoglobin stabilization and RBC-transfusion-independence and changes in the frequency of RBC-transfusions [15–17].

It is not surprising definitions of RBC-transfusion-dependence and improvement or response vary. None of RBC-transfusion criteria cited was developed using a structured method nor are there any studies of internal validation of the non-structured method(s)used. It is also possible that definitions of RBC-transfusion-dependence and -independence or improvement may vary in diverse diseases and disease-settings. Even when there is external validation for an arbitrary definition of RBC-transfusion-dependence and - independence, alternative definitions were not tested.

Structured expert-panel consensus techniques are used to define medical conditions, therapies and terms. These approaches quantify expert opinion and yield definitions that can be internally- and sometimes externally-validated. Recent data indicate reasonably high

levels of agreement amongst experts using these techniques [21]. We used a modified RAND-Delphi consensus panel technique to define RBC-transfusion-dependence and -independence using a panel of expert hematologists from North America and Europe [22–29].

2. Method

We developed a 10 question instrument focused on defining RBC-transfusion dependence and -independence (Fig. 1). The questionnaire was distributed by e-mail to each of the 17 expert hematologists selected for diversity of age, gender, specialization, professional setting and geography. Each expert was asked to anonymously score their answers on the instrument which was returned to the panel leader (nonvoting) by e-mail. Answers were collated and a revised instrument indicating each panelists' scoring re-distributed to the experts at a face-to-face meeting 3 weeks later. At this meeting the distribution of answers to each question was discussed without identifying the respondent and panelists invited to comment, cite supporting published and unpublished data, personal experiences and biases. Panelists were asked to again anonymously score their answers on the collated questionnaire which were collected and analyzed by the panel leader. Mean and variance (standard deviation) for each question was determined. For no/yes questions, no was assigned a value of 0 and yes a value of 1. Mean score and standard deviation was reported (Fig. 1). Results presented below are after round-2.

3. Results (Table 1)

3.1. RBC-transfusion dependence

Panelists considered a 3-month interval (3.2 ± 0.24 months) to be the shortest appropriate surveillance interval to define a person as RBC-transfusion-dependent. They considered an average transfusion volume of 2U RBC/month (1.92 ± 0.08 U/month) over this interval to be the most appropriate frequency of RBC-transfusions to define a person as RBC-transfusion-dependent.

3.2. RBC-transfusion-independence

Panelists considered a 3-month interval (2.93 ±0.23) to be the shortest appropriate surveillance interval to define a person as being RBC-transfusion-independent after and interval of having been RBC-transfusion-dependent. They did not consider it appropriate (0.29 ±0.22) to also require a minimum hemoglobin level in addition to RBC-transfusion-independence to define a person as RBC-transfusion-independent. Nor did they consider it appropriate (0.13 ±0.11) to require a minimum hemoglobin increase from baseline in addition to RBC-transfusion-independence to define a person as RBC-transfusion-independent.

3.3. Decrease in RBC-transfusion-dependence

In addition to RBC-transfusion-independence as defined above, panelists considered (0.93 ± 0.07) a 50% (52% ± 7) reduction in RBC-transfusion frequency a valid endpoint for anemia response in persons defined RBC-transfusion-dependent as above.

4. Discussion

We used a modified RAND-Delphi consensus panel technique to define RBC-transfusion-dependence and improvement or - independence. In addition to RBC-transfusion-independence, we found experts considered a 50% reduction in RBC-transfusions in persons with prior RBC-transfusion-dependence as defined herein to be an appropriate indicator of an anemia response. There was little disagreement amongst experts when questions were clearly stated, when there was an appropriate scale of possible responses, when scoring was anonymous when successive rounds of voting and when there was data-sharing between voting rounds. This agrees with results of other RAND-Delphi studies of therapy-interventions in diverse hematological and non-hematological diseases like cardio- and cerebro-vascular diseases, coronary bypass surgery, carotid endartectomy and endoscopy [27]. Although most data presented to experts were from studies of MDS and MPNs, results of our analyses may apply to other disorders like aplastic anemia.

These definitions differ substantially from those suggested by unstructured consensus panels and those arbitrarily-defined by investigators in specific diseases or disease-therapy trials. Others may want to consider using these definitions and/or comparing them with current definitions of RBC-transfusion-dependence and -independence. A study of external validation of these definitions is in progress.

Another point is many of the guidelines and criteria cited above, like the IWG 2000 guidelines for MDS, use the term “transfusion” without specifying the type (RBC, platelet, granulocyte) or volume or number (1 U, 2U, etc.). For purposes of this report we considered such statements to indicate 1 U RBC-transfusion. We suggest greater precision in using “transfusion” in future guidelines and criteria. Also, most guidelines specifying U of RBC-transfusions focus on adults assumed to be 70 kg in whom 1 U RBC is assumed to be 350 ml. This is not always accurate. The theoretical dose translates to a dose of 5 ml/kg. However, in children a more typical RBC-transfusion dose is 10 ml/kg. Consequently, our and other recommendations for defining RBC-transfusion dependence should be adjusted when used in children.

Results of our study are intended for use in an operational context, especially in the conduct and evaluation of clinical trials. They are likely to be controversial when considered in other contexts. For example, we do not suggest persons receiving 1 U RBC every 28 day are not RBC-transfusion-dependent; clearly they are. However, the need for a consensus definition to evaluate new therapies, and enable comparison of prognostic scoring systems and clinical trials data is clear. Also, although there is consensus in this study as to the hemoglobin level persons should receive a RBC-transfusion, this is based on a defined clinical setting where panelists were asked to envision the “average” subject requiring RBC-transfusions. The question was asked in the context of determining whether a RBC-transfusion should be scored in calculating whether a subject is RBC-transfusion-dependent. Clinical settings outside the context of a consensus study will inevitably encompass subjects who are not “average” and in whom RBC-transfusions may be given (whether needed or not) at higher and lower hemoglobin levels. Moreover, this hemoglobin level is not proposed as a guideline for the decision as to whether or not to give a RBC-transfusion to a subject.

These consensus conclusions may be useful in defining persons who are RBC-transfusion-dependent and -independent, in comparing prognostic scoring systems and in designing and executing clinical trials of drugs designed to reverse RBC-transfusion-dependence in blood and other disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Thank you to Ms. Sabine Jacob who prepared the manuscript. Ms. Jill Kueser organized the questionnaires, mailings and meetings.

References

[1]. Jadersten M, Malcovati L, Dybedal I, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. J Clin Oncol 2008;26:3607–13. [PubMed: 18559873]

[2]. Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood 2008; 111:574–82. [PubMed: 17940203]

[3]. Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Br J Haematol 2003;120:1037–46. [PubMed: 12648074]

[4]. Palmer SC, Navaneethan SD, Craig JC, et al. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. Ann Intern Med 2010;153:23–33. [PubMed: 20439566]

[5]. Rizzo JD, Somerfield MR, Hagerty KL, et al. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology 2007 clinical practice guideline update. J Clin Oncol 2008;1:132–49.

[6]. Malcovati G, Germin U, Kuendgen A, et al. Time dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol 2007;25:3503–10. [PubMed: 17687155]

[7]. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419–25. [PubMed: 16609072]

[8]. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 2006:24:3895–903. [PubMed: 16921040]

[9]. Lyons RM, Cosgriff TM, Modi SS, et al. Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. J Clin Oncol 2009;27:1850–6. [PubMed: 19255328]

[10]. Cerma kJ, Kacirkova P, Mikulenkova D, et al. Impact of transfusion dependency on survival in patients with early myelodysplastic syndrome without excess of blasts. Leuk Res 2009;33:1469–74. [PubMed: 19646756]

[11]. Tefferi A, Barosi G, Mesa RA, et al. IWG for Myelofibrosis Research and Treatment (IWG-MRT) International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). Blood 2006:108:1497–503. [PubMed: 16675707]

[12]. Tefferi A, Siragusa S, Hussein K, et al. Transfusion at presentation and its acquisition in the first year of diagnosis are both equally detrimental for survival in primary myelofibrosis - prognostic

relevance is independent of IPSS or karyotype. Am J Hematol 2010;85:14–7. [PubMed: 20029953]

[13]. Tefferi A JAK2 mutations and clinical practice in myeloproliferative neoplasms. Cancer J 2007;13:366–71. [PubMed: 18032973]

[14]. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood 2009;26(113):2895–901.

[15]. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood 2010; 115(9): 1703–8. [PubMed: 20008785]

[16]. Porter J, Galanello R, Saglio G, et al. Relative response of patient with myelodysplastic syndromes and other transfusion-dependent anaemias to deferasirox (ICL670): a 1-yr prospective study. Eur J Haematol 2008;80:168–76. [PubMed: 18028431]

[17]. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuaria. N Engl J Med 2006;355:1233–43. [PubMed: 16990386]

[18]. Hill A, Hillmen P, Richards SJ, et al. Sustained response and longterm safety of eculizumab in paroxysmal nocturnal hemoglobinuria. Blood 2005;106:2559–65. [PubMed: 15985537]

[19]. Hillmen P, Hall C, Marsh JC, et al. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med 2004;350:552–9. [PubMed: 14762182]

[20]. Cheson BD, Greenberg PL, Bennett J, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419–25. [PubMed: 16609072]

[21]. Shekelle PG, Kahan JP, Bernstein SJ, et al. Reproducibility of the method to identify the overuse and underuse of medical procedures. N Engl J Med 1998;388:1988–95.

[22]. Winslow CM, Solomom DH, Chassin MR, et al. The appropriateness of carotid endartectomy. N Engl J Med 1988;318:721–7. [PubMed: 3279313]

[23]. Park RE, Fink A, Brook RH, et al. Physician ratings of appropriate indications for six medical and surgical procedures. Am J Pub Health 1986;76:766–72. [PubMed: 3521341]

[24]. Brook RH. The RAND/UCLA appropriateness method. In: McCormick KA, Moore SR, Siegel RA, editors. Clinical practice guideline development: methodology perspectives. Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, Office of the Forum for Quality and Effectiveness in Health Care; 1994 [Pub. No. 95–0009; also available as Brook RH. The Rand/UCLA appropriateness method: Rand/RP-395. Santa Monica, CA: Rand Corporation, 59–70],

[25]. Merrick NJ, Fink A, Park RE, et al. Derivation of clinical indications for carotid endarterectomy by an expert panel. Am J Pub Health 1987;77:187–90. [PubMed: 3799858]

[26]. Shekelle PG, Chassin MR, Park RE. Assessing the predictive validity of the RAND/UCLA appropriateness method criteria for performing carotid endarterectomy. Inti J Tech Assess Health Care 1998;14:707–27.

[27]. Shelby JVB, Fireman BH, Lundstrom RJ, et al. Variation among hospitals in coronary-angiography practices and outcomes after myocardinal infarction in a large health maintenance organization. N Engl J Med 1996;335:1888–96. [PubMed: 8948565]

[28]. Kravitz RL, Laouri M, Kahan JP, et al. Validity of criteria used for detecting underuse of coronary revascularization. J Am Med Assoc 1995;274:632–8.

[29]. Gale RP, Park RE, Dubois R, Bitran J, Buzdar A, Hortobagyi G, et al. Delphi-consensus panel analysis of appropriateness of high-dose chemotherapy and blood cell or bone marrow autotransplants in women with breast cancer. Clin Transplant 2000;14:32–41. [PubMed: 10693633]

Table 1

Delphi expert-consensus panel definitions of RBC-transfusion-dependence and - independence.

	RBC-transfusions	Surveillance interval
RBC-transfusion-dependence	≥2 U/month	3 months
RBC-transfusion-independence	None	3 months
Reduced RBC-transfusion-dependence	50% decrease	3 months