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What are RBC-transfusion-dependence and -independence?

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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.

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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 ≥ 1 U 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 ≥ 1 U 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% CI: 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 ≤ 90 g/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 >2 U 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 ≥ 2 U RBC for 28 days for a hemoglobin <85 g/l [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 ≥ 8 U 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 ≥ 1 U 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 ≥ 4 U decrease in RBC-transfusion frequency (given for a hemoglobin level ≤ 90 g/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 ≥ 20 g/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/l [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 (non-voting) 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 2 U 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% ($52\% \pm 7$) 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

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

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