Red blood cell transfusions in hemato-oncological patients: Don't iron out the consequences

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RED BLOOD CELL TRANSFUSION SUPPORT AND MANAGEMENT OF SECONDARY IRON OVERLOAD IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES IN THE NETHERLANDS: A SURVEY

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Abstract

Background and objectives: Evidence-based guidelines on optimal triggers for red blood cell (RBC) transfusion in patients with hematological malignancies exist, but the evidence is weak. Secondary iron overload is an often overlooked chronic complication of RBC transfusions and also here guidelines are either lacking or lack international consensus. Our aim was to evaluate the triggers for RBC transfusion support and management of secondary iron overload among hematologists in the Netherlands.

Materials and methods: For this cross-sectional study, all hematologists and hematologists in training in the Netherlands were sent a web-based, 25-question survey including three clinical scenarios. The survey distribution took place between November 19, 2015 and January 26, 2016.

Results: Seventy-seven responses were received (24%), well distributed among community and university hospitals. A wide variation in hemoglobin triggers existed: 5.6-9.5 g/dL (median: 8.0 g/dL). Personalization of this trigger was mostly based on (estimated) cardiopulmonary compensation capacity of patients. About 65% of respondents reported two RBC units per transfusion episode (range 1-3). For monitoring secondary iron overload, serum ferritin was most frequently measured (97%), while a value of 1000-1500 µg/L was the most common cut-off to initiate treatment (39%). For 81% of respondents, phlebotomies were the first choice of treatment, although often the hemoglobin level was considered a limiting factor.

Conclusion: Our results confirm large reported variation in daily practice among hematologists in the Netherlands regarding RBC transfusion support and management of secondary iron overload. Future studies providing better evidence are needed to improve guidelines specific for patients with hematological malignancies.

Introduction

Almost twenty percent of all red blood cell (RBC) transfusions in Europe are given to patients with hematological malignancies to compensate their disease and treatment-related anemia [1,2]. The beneficial effect of these RBC transfusions on e.g. quality of life, bleeding and other clinical outcomes remains however, difficult to quantify [3-5]. While studies on restrictive RBC transfusion strategies show no disadvantages in other patient groups, limited data is available on such strategies in patients with hematological malignancies [5-7]. Hemoglobin triggers and number of RBC units given per transfusion episode may therefore vary in daily practice.

Furthermore, apart from acute transfusion reactions, secondary (transfusion-related) iron overload, a more chronic complication, occurs in many patients with hematological malignancies who undergo hematopoietic stem cell transplantation or are treated for myelodysplastic syndrome (MDS) [8,9]. Secondary iron overload often occurs in patients who received about 20 RBC transfusions, while after 30 RBC transfusions the positive predictive value for significant hepatic iron overload reaches 96% [10,11].

Although the negative impact of iron overload on mortality and morbidity is well established in various patient groups, for instance thalassemia patients [12-14], this remains to be elucidated in patients with hematological malignancies. Recent data suggest inferior overall survival for transfusion-dependent MDS patients as a consequence of secondary iron overload [15,16]. Moreover, patients with hematological malignancies may be more prone to develop iron toxicity-related cardiac disease. Cardiac remodeling, namely, is additionally induced by long-standing anemia and cardiomyopathy by various chemotherapeutical agents [17]. Indeed, cardiac failure is the most common non-leukemic cause of death (51%) among patients with MDS, and fatal cardiac failure is significantly more frequent in transfusion-dependent MDS patients [18].

Furthermore, data on the effect of iron chelation therapy in patients with hematological malignancies are scarce as most studies were executed in small or highly selected patient groups or suffer from serious methodological problems like confounding by indication [16, 19-21].

In summary, for optimal RBC transfusion strategies for patients with hematological malignancies as well as monitoring and treatment of secondary iron overload, high-grade evidence is unavailable. As a result, we assumed a wide variation in the daily practice of RBC support and management of iron overload in the Netherlands.

The aim of the current study was to evaluate RBC transfusion support and management of secondary iron overload in patients with hematological malignancies among hematologists and hematology trainees in the Netherlands by means of an online survey.

Materials and methods

In this cross-sectional study, all hematologists and hematologist trainees in the Netherlands were asked to complete a structured, 25-question online survey. The questions related to clinical factors influencing initiation of RBC transfusion, numbers of RBC units given per transfusion episode, and clinical factors influencing detection and management of secondary iron overload regarding adult patients with hematological malignancies. Additionally, three clinical scenarios were presented in order to test consistency of replies with the previous responses to similar questions. For questions with a quantitative nature, a 5-point Likert scale was used (never, sometimes, regularly, often, always) [22]. The complete survey is provided in the supplementary material. Incomplete surveys were included in the analysis.

This web-based survey was approved by the members of the working party "non-oncological hematological diseases" of the Dutch Hematology Association and was distributed by email. The survey distribution included one reminder and took place between November 19, 2015 and January 26, 2016.

In order to guard anonymity, participants were not asked for identifying information such as age and gender. No incentives were provided.

Descriptive statistical methods (frequencies and histograms) were used for the analyses using IBM SPSS statistics, version 23 (Armonk, NY: IBM Corp.).

Results

Study cohort

In total, of 325 sent surveys, 77 responses were received (24%). The respondents represented all eight university hospitals and 29 community hospitals (39%) across the Netherlands. Ninety-nine percent of the respondents attended relevant hematology conferences, either European, American or Dutch in the preceding three years; whereas only 20% attended specific conferences on transfusion medicine in the preceding three years. According to respondents, 14 out of 37 institutions

(38%) employed an in-house consultant in transfusion medicine and 18% of the respondents reported being a transfusion medicine consultant.

RBC transfusion triggers

Sixty-six percent of the responders, representing 27 centers, reported existing institutional RBC transfusion guidelines specific for patients with hematological malignancies.

Table 1 shows the reported hemoglobin triggers for hemodynamically stable, hospitalized patients and outpatients without severe co-morbidities. The triggers ranged from 5.6 to 9.5 g/dL (median 8.0 g/dL). For hemodynamically stable hospitalized patients, the most frequently reported hemoglobin trigger was 8.0 g/dL (42%) and for outpatients 7.2 g/dL (34%).

Table 1

Hemoglobin trigger g/dL	(mmol/L)	Hospitalized patients number (%)		Outpatients number (%)	
< 5.6	(<3.5)	1	(1)	0	(0)
6.4	(4.0)	1	(1)	6	(8)
7.2	(4.5)	17	(22)	26	(34)
8.0	(5.0)	32	(42)	24	(31)
8.8	(5.5)	16	(21)	20	(26)
9.6	(6.0)	10	(13)	1	(1)
Total		77	(100)	77	(100)

Reported hemoglobin triggers for hemodynamically stable hospitalized patients and outpatients without severe comorbidities

The number of RBC units given per transfusion episode for hospitalized patients and outpatients is depicted in figure 1. Most commonly, two RBC units were given per transfusion episode (range 1-3). Additionally, 16% of all respondents considered weight and/or total blood volume when ordering a specific number of RBC units.

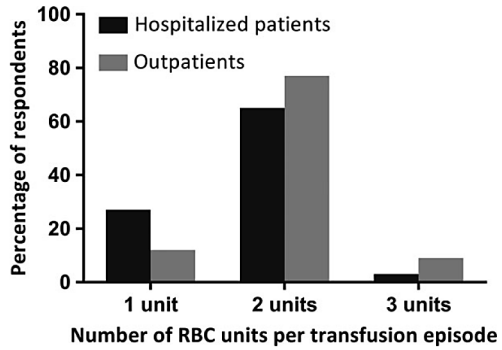

Figure 1 Number of RBC units per transfusion episode.

RBC: Red Blood Cell.

Figure 2 shows a subset of clinical factors possibly influencing the hemoglobin trigger for RBC transfusion. A higher hemoglobin level was maintained after recent cardiac ischemia or cardiac failure (New York Heart Association (NYHA) grade II-IV). In this respect, also higher age, dyspnea, signs of hypoxia, bleeding with or without accompanied thrombocytopenia, and quality of life were often considered by the respondents.

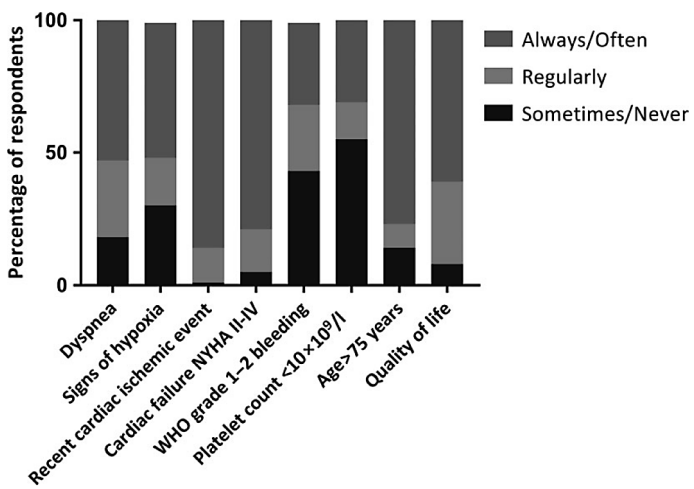

Figure 2 Clinical factors influencing RBC transfusion initiation.

NYHA: New York Heart Association; WHO: World Health Organization.

Particularly in the outpatient setting, various logistic reasons caused non-adherence to a common trigger. Difficulties to organize an outpatient transfusion appointment, the travel time for the patient to the hospital and the time between appointments, played a role in 64%, 71%, and 75% of the respondents, respectively. RBC transfusions in the neutropenic phase during intensive chemotherapy or hematopoietic stem cell transplantation will be guided and dependent on measurements of the complete blood count. The frequency of measurement of these blood counts, varied considerably from once or twice a week in 7% of respondents, three to four times a week in 58%, to five to seven times a week in 35%. Besides hemoglobin level, 17% of the respondents performed additional tests to determine whether RBC transfusion was required. Of these respondents, 20% considered the patient's vital signs, 20% serum ferritin levels, whereas 60% considered the hemoglobin increment after previous RBC transfusions to guide further transfusion.

Monitoring of secondary iron overload

Twenty-six percent of the respondents reported to comply with a local guideline regarding detection and treatment of iron overload and 61% reported to comply to the national guideline [23]. Three respondents reported to comply with the national as well as a local guideline.

Factors that led respondents to initiate monitoring of secondary iron overload were: the total RBC transfusion burden (77%, [20-29 RBC units, 58%]), a transfusion intensity of ≥2 RBC units per month (52%), and a hematopoietic stem cell transplantation in the medical history (46%).

Figure 3 shows the iron parameters used by the respondents to monitor iron overload. Serum ferritin (97%) was the most frequently measured iron parameter, either alone (55%) or in combination with C-reactive protein (43%). Additional diagnostic tests that were reported included: transferrin saturation, serum iron, total iron-binding capacity, and bone marrow iron staining. Forty-two percent of all respondents never performed the currently available, most specific tests for iron overload: a biopsy of liver or myocardial tissue or a T2* MRI of heart and/or liver, while 58% considered one of these additional tests.

For the 58% of respondents who performed a MRI or biopsy, the following indications were mentioned (multiple answers were possible): an elevated serum ferritin level (44%, with most reported cut-off values of 1000-1500 µg/L [38%] and 1500-2000 µg/L [24%] respectively), increased liver enzymes (46%), decreased liver function (e.g. low serum albumin levels, disturbed production of coagulation

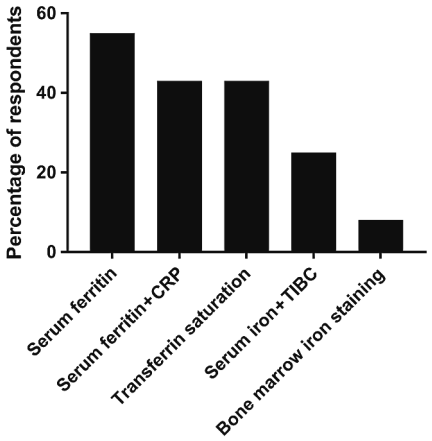

Figure 3 Iron parameters used in the detection of iron overload.

CRP: C-reactive protein; TIBC: total iron binding capacity.

factors [26%]), occurrence of cardiac failure (27%), or endocrinopathy (14%). Unexplained fatigue, arthromyalgia, bronze skin, transfusion intensity, total RBC transfusion burden, and cardiac arrhythmia in the absence of inflammation were less common reasons for performing additional diagnostic tests for secondary iron overload.

Management of iron overload

Figure 4 shows determining factors for treatment of secondary iron overload. For most of the respondents, the serum ferritin level was the reason to start treatment (86%). A serum ferritin level of 1000-1500 µg/L (39%), 1500-2000 µg/L (21%), and 2000-2500 µg/L (24%) were the most commonly reported cut-off values. For 75% of respondents, a total RBC transfusion burden of 20-29 units was reason to initiate iron overload treatment.

For 81% of all respondents, phlebotomies were the first choice for treating iron overload when hemoglobin levels were sufficiently high. Conversely, iron chelation therapy was the first choice in 20% of respondents. In all respondents (multiple answers possible), deferasirox was the most commonly prescribed iron chelation agent (91%), followed by deferiprone (9%), and deferoxamine (5%). Nine percent of all respondents never prescribed iron chelation therapy. The hemoglobin level was the most important clinical factor influencing the choice of treatment (phlebotomy versus iron chelation; 87%). Factors influencing this treatment choice are summarized in figure 5.

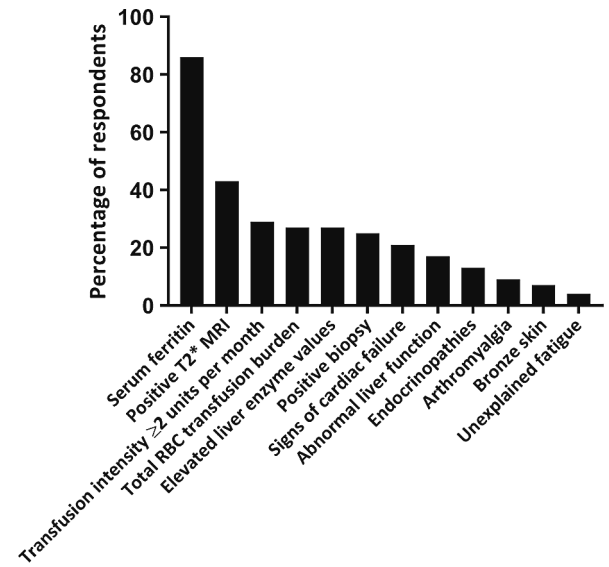

Figure 4 Clinical and laboratory factors for initiating management of secondary iron overload.

MRI: Magnetic Resonance Imaging; RBC: Red Blood Cell.

Reasons to refrain from starting iron chelation therapy in spite of a high serum ferritin level were (multiple answers possible): comorbidity limiting prognosis (75%), limited life expectancy of less than one year (70%) or less than three years (41%), age ≥85 years (49%), renal dysfunction (50%), possible side effects (26%), drug-drug interactions (25%), reduced quality of life (20%), expected lack of treatment compliance (16%), and costs (3%).

The most frequently reported reasons for cessation of iron chelation therapy were: a dismal prognosis (46%), side effects/intolerance (38%), and comorbidity (13%), but also reaching a certain low serum ferritin level (71%, [500 µg/L 93%]) and transfusion-independency (26%) were reasons to stop. On the contrary, twenty-five percent of the respondents state that –once started– they usually do not stop iron chelation therapy.

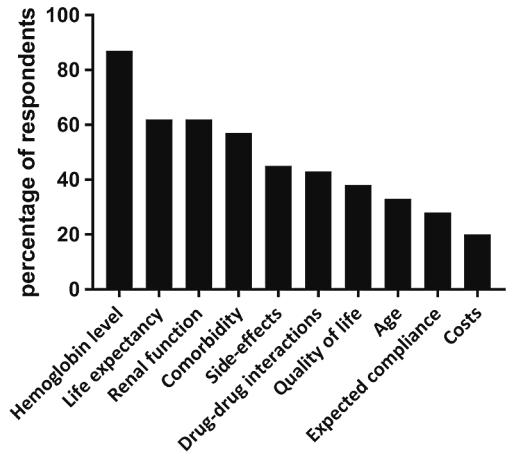

Figure 5 Clinical factors influencing treatment choice in management of iron overload

Discussion

This survey among hematologists and hematologist trainees in the Netherlands shows large reported variation in daily practice, not only regarding RBC transfusion support but also for the monitoring and management of secondary (transfusion-associated) iron overload in patients with hematological malignancies.

First, hemoglobin triggers for RBC transfusion differed among the respondents. For hemodynamically stable, hospitalized patients, a hemoglobin level of 8.0 g/dL (5 mmol/L) was the most commonly reported trigger. For outpatients this was 7.2 g/dL (4.5 mmol/L). However, the range varied considerably from 5.6 g/dL up to 9.6 g/dL. Patient-specific adaptation of these triggers by the respondents was mostly based on the (estimated) cardiopulmonary compensation capacity and age. These triggers may be derived from the RBC transfusion triggers for normovolemic anemia patients with an acute bleeding according to the Dutch transfusion guideline, the so-called '4-5-6 rule' in which a RBC transfusion is initiated at a hemoglobin trigger of 6.4 g/dL (4 mmol/L) in young and otherwise healthy patients. This trigger is adjusted to 8.0 g/dL or 9.6 g/dL (5 mmol/L or 6 mmol/L) dependent on comorbidities and other clinical factors [7]. However, the observed variation of hemoglobin triggers, reported in our survey, is much wider.

Second, when initiating a RBC transfusion, the number of RBC units given per transfusion episode also differed widely among the respondents. Interestingly, in a more concrete clinical setting simulated by *clinical scenario 1 and 2 (supplementary textbox 1 and 2)*, respondents initiate RBC transfusion at a higher hemoglobin trigger than the responses in the survey suggest. Moreover, respondents tended to transfuse more RBC units per transfusion in the scenario setting than was reported in the survey.

These differences in RBC transfusion practice, either hemoglobin triggers or number of RBC units per transfusion episode, likely originate from a lack of high-grade evidence-based guidelines for this specific group of patients. Interestingly, often a less restrictive transfusion policy is applied in actual patients. This is probably due to the widespread believe that a high hemoglobin level is beneficial for patients according to the '10/30-rule' introduced in 1942, in which a RBC transfusion was suggested in surgical patients when the hemoglobin levels drops below 10 g/dL or the hematocrit below 30% [24]. The variation in hemoglobin triggers in our study are also in line with a recently published survey regarding RBC transfusion practice in leukemia patients in the United States [25]. Although for the present study, the outpatient hemoglobin levels were slightly lower when compared with the inpatient hemoglobin triggers, which is in contrast to the US study. The travel distance to hospitals for outpatients in the Netherlands is probably much shorter, which facilitates a more restrictive transfusion approach in the outpatient setting. Nevertheless, both our study as well as the US study suggest at least the risk for over-transfusion in these patients, while a recent meta-analysis performed by our group suggests no differences in mortality rates and safety outcomes when applying more restrictive RBC transfusion strategies compared with more liberal strategies in patients with hematological malignancies [26].

Currently, a number of studies on RBC transfusion triggers and iron overload monitoring and treatment in patients with hematological malignancies are being carried out. For example, the preliminary results from the randomized, controlled TRIST study, comparing a restrictive (7 g/dL) and a liberal (9 g/dL) hemoglobin trigger, suggest no differences in quality of life and other clinical outcomes in patients with hematological malignancies undergoing hematopoietic stem cell transplantation [27]. Many more studies on RBC transfusion strategies in patients with hematological malignancies (REDDS ISRCTN26088319; EnhanceRBC NCT02099669; 1versus2CGR NCT02461264; REAL study ISRCTN 96390716) and studies on efficacy of iron chelation therapy (TELESTO NCT00940602; EUMDS registry NCT00600860) are ongoing. With the results of these studies, we will gain better insight into transfusion triggers and iron overload monitoring and

treatment in one of the most frequently transfused patient groups, namely patients with hematological malignancies.

Besides, reduced RBC use may lead to a decrease in transfusion-associated complications like secondary iron overload. One unit of RBC contains 200-250 mg of iron and thus over 100 times the physiological uptake of 1-2 mg per day by the gut. Frequent RBC transfusions in these already vulnerable patients may therefore lead to iron-mediated toxic effects.

In our study, the most important reasons for the respondents to initiate monitoring of secondary iron overload were: a total RBC transfusion burden of 20-29 units and a transfusion intensity of ≥2 RBC units per month. The total RBC transfusion burden of 20-29 units is similar to the Dutch guideline for patients with myelodysplastic syndromes [23], clearly basing iron overload monitoring on a high net iron dose received as RBC transfusions. Additionally, although not an ideal marker for monitoring iron overload, serum ferritin is the most frequently used biomarker. The combination of serum ferritin levels with a normal level of C-reactive protein, will improve the sensitivity to demonstrate secondary iron overload, since it rules out a high serum ferritin level due to an acute phase reaction. Transferrin saturation, another biomarker for iron body stores, could be most useful for defining the site of iron overload. High values, ≥70% for women and ≥80% for men, namely suggest parenchymal (toxic) iron loading, whereas normal values can indicate reticulo-endothelial iron loading [28].

Additionally intriguing is the fact that the most sensitive and specific tests for secondary iron overload such as T2*MRI or a tissue biopsy of heart and/or liver, are not considered by 42% of the respondents [28]. Possibly, T2* MRI is not widely available, but understandably, tissue biopsies of liver and heart, are less likely to be performed due to its risk of complications in these vulnerable patients.

For most hematologists, phlebotomies were regarded as the first choice iron-lowering therapy (81%). Again, the survey results seem to be discordant with the responses provided in *clinical scenario 3 (supplementary textbox 3)*, in which much less respondents (54%) preferred phlebotomies over iron chelation therapy (46%). This may be explained by the hemoglobin level in the scenario, but also the lack of consensus to guide therapy, is a likely explanation. Iron chelation therapy, of course, has some clear advantages in daily practice. It can be administered orally, whereas phlebotomies are more invasive and require more time and effort from the hospital personnel. However, side effects of iron chelation therapy as well as its costs should also be considered.

Limited life expectancy and limited prognosis due to comorbidity were the most common reasons for our respondents to refrain from iron chelation therapy in case of iron overload in this specific patient group. This was also seen in an European survey among physicians treating transfusion-dependent MDS patients [29]. A serum ferritin level of ≤ 500 µg/L was a general threshold for stopping iron chelation therapy (93% of respondents), whereas clinical and laboratory factors such as normalizing liver or cardiac function were not. Next to limited drug efficacy, a dismal prognosis and side effects/intolerance were the most common reasons to stop iron chelation therapy.

Strengths and limitations:

This is the first large survey among hematologists and hematologist trainees in the Netherlands in which important questions regarding RBC transfusion support and diagnosis and management of secondary iron overload in patients with hematological malignancies are addressed.

The limitation inherent to most surveys is the moderate response rate. However, we consider our survey's response rate quite reasonable with a representation of all eight university hospitals, which treat the majority of patients with hematological malignancies, and 39% of all community hospitals. Second, not all hematologists in the Netherlands treat patients with hematological malignancies. However, we were not able to differentiate this from the available email addresses, so the actual response rate is somewhat underestimated.

Thirdly, the results of the survey for practicing hematologists and hematologists in training were not separated. It is possible that some of the variation found in this study, could be due to this fact.

Furthermore, no actual data on clinical practice were collected. So in theory, the responses reported in the survey and the actual clinical practice could differ. Since all responses were anonymized and we tested the responses in the survey with the results of the clinical scenarios, this is not expected to be a major problem.

Finally, as in all surveys, response bias cannot be excluded. The relatively high amount of transfusion medicine consultants (18%) indicates that such a selection indeed exists in our survey; still this would rather result in an underestimation of the existing variability in daily practice.

In conclusion, the results of this survey indicate large reported variation in RBC transfusion support and assessment and management of transfusion-associated iron overload in Dutch patients with hematological malignancies. Proper evidence-based guidelines on these subjects may reduce this variability.

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Supplementary material

S1 Survey

Dear colleague,

In the context of a PhD research project, we would like to ask you to complete a survey. The aim of this survey is to evaluate the daily practice of red blood cell transfusion support and management of secondary iron overload in the Netherlands.

The survey is approved by the members of the working party 'non-oncological hematological diseases of the Dutch Hematology Association.'
We will ask you in which center you are employed in order to look at differences between centers, these data will be anonymized.

The survey will take 10-15 minutes to complete. You can start the survey by clicking on the link below:
https://response.questback.com/stichtingsanquinbloedvoorzieni/dagelijkse-praktijkerytrocytentransfusie

Thank you for your cooperation!

Used abbreviations

ASA: American Society of Anesthesiology; NYHA: New York Heart Association; WHO: World Health Organization; RBC: Red Blood Cell; AST: Alanine transaminase; GGT: Gamma-glutamyl transpeptidase; T2* MRI: transversal relaxation magnetic resonance imaging.

Remarks

The original survey is in Dutch, this is a translated version.
Mmol/L were converted to g/dL for the manuscript.

1. In which treatment center are you currently employed?

2. Which of the following congresses did you attend in the preceding three years?
   Multiple answers possible.
   - ☐ European Hematology Association congress
   - ☐ American Society Hematology congress
   - ☐ International Society of Thrombosis and Hemostasis congress
   - ☐ International Society of Blood Transfusion congress
   - ☐ Dutch Hematology congress
   - ☐ European Bone Marrow Transplantation congress
   - ☐ Other: American Association of Blood Banks congress, World Federation of Hemophilia congress, European Association of Hemophilia and Allied Disorders congress
   - ☐ None of the above

3. Does your center employ an in-house consultant in transfusion medicine?
   - ☐ Yes
   - ☐ No
   - ☐ I don't know

4. Are you a transfusion medicine consultant yourself?
   - ☐ Yes
   - ☐ No

5. Does your center have institutional guidelines on RBC transfusion support specific for hemato-oncological patients?
   - ☐ Yes
   - ☐ No
   - ☐ I don't know

6. Do you comply with a guideline for the management of secondary iron overload?
   - ☐ Yes; a local guideline
   - ☐ Yes; a national guideline
   - ☐ Yes; an international guideline
   - ☐ No

   - ☐ I don't know
   - ☐ If yes, please specify which guideline you comply with.

7a. At which hemoglobin level do you usually initiate a red blood cell transfusion in a hemodynamically stable, 45- year-old male patient without significant comorbidities (ASA class I-II) during intensive chemotherapy or hematopoietic stem cell transplantation?
   - ☐ < 3.5 mmol/L
   - ☐ 3.5 to 3.9 mmol/L
   - ☐ 4.0 to 4.4 mmol/L
   - ☐ 4.5 to 4.9 mmol/L
   - ☐ 5.0 to 5.4 mmol/L
   - ☐ 5.5 to 5.9 mmol/L
   - ☐ 6.0 to 6.4 mmol/L

7b. At which hemoglobin level do you usually initiate a red blood cell transfusion in a hemodynamically stable, 45-year-old male patient without significant comorbidities (ASA class I-II) with chronic anemia (e.g. myelodysplastic syndrome) in the outpatient clinic.
   - ☐ < 3.5 mmol/L
   - ☐ 3.5 to 3.9 mmol/L
   - ☐ 4.0 to 4.4 mmol/L
   - ☐ 4.5 to 4.9 mmol/L
   - ☐ 5.0 to 5.4 mmol/L
   - ☐ 5.5 to 5.9 mmol/L
   - ☐ 6.0 to 6.4 mmol/L

8. What factors, next to hemoglobin level and diagnosis/treatment, influence your decision to initiate a red blood cell transfusion?
   Response categories: never, sometimes, regularly, often, always
   - ☐ Dyspnea
   - ☐ Signs of hypoxia (oxygen saturation < 90%; PaO2 <7.8 kPa or <60 mmHg)
   - ☐ Recent ischemic cardiac event (in the previous 3 months)
   - ☐ Tachycardia (>100 beats/minute)
   - ☐ Cardiac arrhythmia
   - ☐ Cardiac failure (NYHA grade II-IV)
   - ☐ WHO grade 1-2 bleeding
   - ☐ WHO grade 3-4 bleeding
   - ☐ Platelet count of $<10x10^9$/L without bleeding
   - ☐ Platelet count of $<10x10^9$/L with WHO grade 1-2 bleeding

- ☐ Age ≤40 years
- ☐ Age ≥75 years
- ☐ Age ≥85 years
- ☐ Quality of life
- ☐ Patients' request
- ☐ Hospitalized patient versus outpatient
- ☐ Logistical reasons (e.g. inability to organize an outpatient transfusion appointment)
- ☐ Patients travel distance to hospital
- ☐ Time to next appointment

9. How many times a week is a complete blood count routinely performed in your center in the neutropenic phase during intensive chemotherapy or hematopoietic stem cell transplantation?
   - ☐ Daily
   - ☐ 5 to 6 times a week
   - ☐ 3 to 4 times a week
   - ☐ 1 to 2 times a week
   - ☐ Not applicable
   - ☐ Other, namely:

10. Do you perform additional tests, next to the hemoglobin level, to guide initiation of a red blood cell transfusion?
    - ☐ Yes, namely:
    - ☐ No

11. How many red blood cell units per transfusion episode do you routinely order for a hemodynamically stable, 45-year-old male patient without significant comorbidities (ASA class I-II) during intensive chemotherapy or hematopoietic stem cell transplantation?
    - ☐ 1 unit
    - ☐ 2 units
    - ☐ 3 units
    - ☐ Other, namely:

12. How many red blood cell units per transfusion episode do you routinely order for a hemodynamically stable, 45-year-old male patient without significant comorbidities (ASA class I-II) with chronic anemia (e.g. myelo-dysplastic syndrome) in the outpatient setting.
    - ☐ 1 unit
    - ☐ 2 units
    - ☐ 3 units
    - ☐ Other, namely:

13. Do you consider a patient's weight and/or blood volume to guide red blood cell transfusion support?
    - ☐ Yes
    - ☐ No
    - ☐ I don't know

14. In which patient groups do you perform screening for secondary iron overload, assuming this has consequences for the treatment?
    Multiple answers possible.
    - ☐ All patients who were previously transfused with RBCs
    - ☐ Patients receiving ≥2 RBC per month
    - ☐ Total RBC transfusion burden of 10-19 RBC units
    - ☐ Total RBC transfusion burden of 20-29 RBC units
    - ☐ Total RBC transfusion burden of 30-39 RBC units
    - ☐ Total RBC transfusion burden of 40-49 RBC units
    - ☐ Total RBC transfusion burden of ≥50 RBC units
    - ☐ Patients who underwent intensive (clinical) chemotherapy
    - ☐ Patients who underwent autologous or allogeneic hematopoietic stem cell transplantation
    - ☐ None of the above
    - ☐ Other, namely:

15. What laboratory test(s) would you order when screening for secondary iron overload?
    Multiple answers possible.
    - ☐ Serum ferritin
    - ☐ Serum ferritin in combination with C-reactive protein
    - ☐ Serum iron in combination with total iron binding capacity
    - ☐ Transferrin saturation
    - ☐ Bone marrow iron staining
    - ☐ Other, namely:

16a. What clinical factors influence your decision to perform a MRI T2* and/or biopsy of liver and/or heart?
Multiple answers possible.
- ☐ I have never/rarely performed an MRI and/or biopsy in this respect
- ☐ Certain serum ferritin level
- ☐ Certain total RBC transfusion burden
- ☐ Disturbed liver enzymes (AST, GGT)
- ☐ Disturbed liver function (e.g. ↓ serum albumin levels, ↓ clotting factor production)
- ☐ Signs of cardiac failure
- ☐ Cardiac arrhythmia in absence of inflammation
- ☐ Occurrence of endocrinopathy (e.g. diabetes mellitus type 2, hypothyroidism)
- ☐ Occurrence of unexplained fatigue
- ☐ Occurrence of unexplained arthromyalgia
- ☐ Occurrence of an abnormal brown/bronze skin
- ☐ RBC transfusion intensity ≥2 units/month
- ☐ Other, namely:

When 'certain serum ferritin level' was indicated in question 16a.

16b. What serum ferritin level would lead you to perform a MRI T2* and/or biopsy of liver and/or heart?
- ☐ 500-1000 µg/L
- ☐ 1000-1500 µg/L
- ☐ 1500-2000 µg/L
- ☐ 2000-2500 µg/L
- ☐ 2500-3000 µg/L
- ☐ >3000 µg/L
- ☐ other, namely:

When 'certain total RBC transfusion burden' was indicated in question 16a.

16c. Which total RBC transfusion burden would lead you to perform a MRI T2* and/or biopsy of liver and/or heart?
- ☐ 10-19 RBC units
- ☐ 20-29 RBC units
- ☐ 30-39 RBC units
- ☐ 40-49 RBC units
- ☐ ≥50 RBC units
- ☐ Other, namely:

17a. What factors would lead you to initiate treatment of secondary iron overload?
Multiple answers possible.
- ☐ Certain serum ferritin level
- ☐ Certain total RBC transfusion burden
- ☐ Transfusion intensity ≥2 RBC units/month
- ☐ Disturbed liver enzymes (AST, GGT)
- ☐ Disturbed liver function (e.g. low serum albumin levels, clotting factor production)
- ☐ Signs of cardiac failure
- ☐ Cardiac arrhythmia in absence of inflammation
- ☐ Signs of iron overload on a T2* MRI
- ☐ Signs of iron overload in a liver and/or myocardial biopsy
- ☐ Occurrence of endocrinopathy (e.g. diabetes mellitus type 2, hypothyroidism)
- ☐ Occurrence of unexplained fatigue
- ☐ Occurrence of unexplained arthromyalgia
- ☐ Occurrence of an abnormal brown/bronze skin
- ☐ Other, namely:

When 'certain serum ferritin level was indicated in question 17a.

17b. What serum ferritin level would lead you to initiate treatment for secondary iron overload?
- ☐ 500-1000 µg/L
- ☐ 1000-1500 µg/L
- ☐ 1500-2000 µg/L
- ☐ 2000-2500 µg/L
- ☐ 2500-3000 µg/L
- ☐ >3000 µg/L
- ☐ other, namely:

When 'certain total RBC transfusion burden' was indicated in question 17a.

17c. Which total RBC transfusion burden would lead you to initiate treatment for secondary iron overload?
- ☐ 10-19 RBC units
- ☐ 20-29 RBC units
- ☐ 30-39 RBC units
- ☐ 40-49 RBC units
- ☐ ≥50 RBC units
- ☐ Other, namely:

18a. Can you indicate your preferences regarding treatment of secondary iron overload: phlebotomies when the hemoglobin level is considered sufficiently high?
- ☐ First choice
- ☐ Second choice
- ☐ Not an option

18b. Can you indicate your preferences regarding treatment of secondary iron overload: iron chelation therapy?
- ☐ First choice
- ☐ Second choice
- ☐ Not an option

19. Which clinical factors influence your treatment choice for secondary iron overload?
Multiple answers possible.
- ☐ Hemoglobin level
- ☐ Comorbidity
- ☐ Drug interactions with comedication
- ☐ Renal dysfunction
- ☐ Costs
- ☐ Possible adverse effects
- ☐ Life expectancy
- ☐ Age
- ☐ Expected therapy compliance
- ☐ Quality of life
- ☐ Other, namely:

20. What iron chelating agent(s) do you prescribe to your patients with secondary iron overload?
Multiple answers possible.
- ☐ I never/rarely prescribe iron chelation therapy
- ☐ Deferoxamine (Desferal™)
- ☐ Deferasirox (Exjade™)
- ☐ Deferiprone (Ferriprox™)
- ☐ Other, namely:

21. Which clinical factors would guide your decision to not treat a patient with iron chelation therapy despite a high serum ferritin level?
Multiple answers possible.
- ☐ Limited life expectancy ≤1 year
- ☐ Limited life expectancy ≤3 years
- ☐ Limited life expectancy ≤5 years
- ☐ Age ≥75 years
- ☐ Age ≥85 years
- ☐ Comorbidity limiting prognosis
- ☐ Renal dysfunction
- ☐ Drug interaction with comedication
- ☐ Possible side effects of iron chelation therapy
- ☐ Low quality of life
- ☐ Expected low therapy compliance
- ☐ Costs of iron chelation therapy
- ☐ Other, namely:

22a. Which clinical factors would guide your decision to stop iron chelation therapy?
Multiple answers possible.
- ☐ I usually do not stop iron chelation therapy once it is started
- ☐ Having reached a certain serum ferritin level
- ☐ Normalization of liver values
- ☐ Normalization of cardiac function
- ☐ Normalization of cardiac rhythm
- ☐ Normalization of T2*MRI liver and/or heart
- ☐ Normalization of liver and/or myocardial biopsy
- ☐ Disappearance of endocrinopathy (e.g. diabetes mellitus type 2, hypothyroidism)
- ☐ Disappearance of arthromyalgia
- ☐ Limited life expectancy
- ☐ Having reached transfusion-independency
- ☐ Other, namely:

22b. What serum ferritin level would lead you to stop iron chelation therapy?
- ☐ <500 µg/L
- ☐ <1000 µg/L
- ☐ <1500 µg/L
- ☐ <2000 µg/L
- ☐ <2500 µg/L
- ☐ Other, namely:

Clinical scenario 1

A 23-year-old patient with acute lymphoid leukemia is currently admitted to the hospital for remission-induction chemotherapy. Her hemoglobin level is 4.4 mmol/L. She has no specific complaints and all vital signs are normal. It is likely her hemoglobin level will decrease in the next few days.

23a. Would you initiate a RBC transfusion at this moment?
- ☐ Yes
- ☐ No
- ☐ I don't know

23b. If yes: How many RBC units would you order at this moment?
- ☐ 1 RBC unit
- ☐ 2 RBC units
- ☐ 3 RBC units
- ☐ 4 RBC units
- ☐ Other, namely:

23c. If no: Do you schedule a RBC transfusion for the next day?
- ☐ Yes
- ☐ No
- ☐ I don't know

23d. If yes: How many RBC units would you order for the next day?
- ☐ 1 RBC unit
- ☐ 2 RBC units
- ☐ 3 RBC units
- ☐ 4 RBC units
- ☐ Other, namely:

Clinical scenario 2

A 74-year-old patient with a myelodysplastic syndrome with an excess of blasts (MDS RAEB-1) is known to have a moderate chronic obstructive pulmonary disease (Gold class 2) and peripheral vascular disease. He is treated with demethylating therapy since he is not a candidate for intensive chemotherapy. For treating disease-related anemia, he received 30 RBC units in total. He visits the outpatient clinic to receive the fourth cycle of demethylating therapy. His hemoglobin level is 5.6 mmol/L, he has no specific health complaints and his vital signs are normal.

24a. Would you initiate a RBC transfusion at this moment?
- ☐ Yes
- ☐ No
- ☐ I don't know

24b. Would you initiate a RBC transfusion when his hemoglobin level would be 4.5 mmol/L?
- ☐ Yes
- ☐ No
- ☐ I don't know

24c. Are you going to monitor this patient for secondary iron overload?
- ☐ Yes
- ☐ No
- ☐ I don't know

24d. Would you treat this patient for secondary iron overload if there are signs of secondary iron overload?
- ☐ Yes
- ☐ No
- ☐ I don't know

Clinical scenario 3

A 58-year-old patient recently underwent an allogeneic stem cell transplantation due to a myelodysplastic syndrome with an excess of blasts (MDS RAEB 2). His total RBC transfusion burden is 50 units. His hemoglobin level is currently 6.8 mmol/L; his serum ferritin level is 3500 µg/L. There are no signs of active infection, inflammation or cardiac failure. All liver enzyme values are within normal ranges.

25a. Do you consider treatment for secondary iron overload at this moment?

- ☐ Yes
- ☐ Only if a T2* MRI or biopsy of liver and/or heart indicates iron overload
- ☐ No
- ☐ I don't know

25b. If you chose 'only if a T2* MRI or biopsy of liver and/or heart indicates iron overload': What treatment would you prefer?

- ☐ phlebotomies
- ☐ Iron chelation therapy
- ☐ Other, namely:

Supplementary textbox 1

Clinical scenario 1

A 23-year-old patient with acute lymphoid leukemia is currently admitted to the hospital for remission-induction chemotherapy. Her hemoglobin level is 7.1 g/dL. She has no specific complaints and all vital signs are normal. It is likely her hemoglobin level will decrease in the next few days.

Thirty-five percent of the respondents would, at this point, give this patient a RBC transfusion. Two RBC units would be ordered by 74% of these respondents, followed by one RBC unit in 15% and three RBC units in 11% of respondents. Of the 65% who would not immediately give a RBC transfusion, 14% would order a RBC transfusion for the next day. In case the patients' hemoglobin level would be 6.5 g/dL, 94% of the respondents would give a RBC transfusion right away. Sixty-two percent would order 2 RBC units for this transfusion episode, 22% one unit, 15% three units and 1% four units for a single transfusion episode.

Supplementary textbox 2

Clinical scenario 2

A 74-year-old patient with a myelodysplastic syndrome with an excess of blasts (MDS RAEB-1) is known to have a moderate chronic obstructive pulmonary disease (Gold class 2) and peripheral vascular disease. He is treated with demethylating therapy since he is not a candidate for intensive chemotherapy. For treating disease-related anemia, he received 30 RBC units in total. He visits the outpatient clinic to receive the fourth cycle of demethylating therapy. His hemoglobin level is 8.9 g/dL, he has no specific health complaints and his vital signs are normal.

Ninety-two percent of the respondents would not initiate a RBC transfusion at this point, while 97% of all respondents would if his hemoglobin level were 7.3 g/dL. Screening for secondary iron overload was considered by 59% of the respondents; 49% would treat in case of secondary overload (according to local guidelines), whereas 26% would only treat in case of iron overload specific complaints. Surprisingly, 20% of the respondents who performed screening, would eventually not treat this patients for secondary iron overload (5% of respondents did not know yet whether to treat him or not.

Supplementary textbox 3

Clinical scenario 3

A 58-year-old patient recently underwent an allogeneic stem cell transplantation for a myelodysplastic syndrome with an excess of blasts (MDS RAEB 2). His total RBC transfusion burden is 50 units. His hemoglobin level is currently 10.8 g/dL; his serum ferritin level is 3500 µg/L. There are no signs of active infection, inflammation or cardiac failure. All liver enzyme values are within normal ranges.

At this point, 88% of the respondents consider iron lowering therapy, of whom 17% would first perform an additional T2*MRI and/or a liver or heart biopsy to determine the presence of iron overload. From the 88% of respondents considering iron lowering therapy, 54% would choose for phlebotomies and 46% for iron chelation therapy.