Clinical characteristics and management of iron overload in 631 patients with chronic transfusion dependency: results from a multicentre, observational study

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Background. Long-term red blood cell transfusion therapy results in iron overload. Consensus documents have been developed for several transfusion-dependent groups of patients to provide clinicians with guidance on the monitoring and treatment of this transfusion complication. The objective of this study was to describe the clinical characteristics and current standard of care for patients with transfusion dependency in Spain.

Material and methods. This observational, multicentre study was conducted from November 2008 to December 2009 in 41 Spanish hospitals and day-care centres. Patients who received their first transfusion after January 2007, and who had received at least 10 units of packed red blood cells at the time of inclusion were eligible for the study.

Results. We collected data from 631 patients with a mean age of 65±17 years. Haematological disease (84% of patients) was the most frequent underlying disorder. Patients had received a mean of 30±26 red blood cell units from diagnosis until inclusion in the study, and a mean of 18±18 red blood cell units in the previous year. Ferritin levels were available before and after starting the study for 116 (18%) and 412 (65%) patients, respectively. Mean ferritin level at study inclusion was 1,570 ng/mL, and 58% of patients had a ferritin level of at least 1,000 ng/mL. In spite of this, only 89 (14%) patients were receiving chelation therapy.

Discussion. The management of patients with transfusion dependency could be improved by using ferritin levels to diagnose iron overload and guide the timely start of chelation therapy.

Keywords: transfusion dependency, chelation therapy, observational study, iron overload.

Introduction

Patients with chronic anaemia resulting from conditions such as aplastic anaemia, thalassaemia syndromes, myeloproliferative neoplasms, and myelodysplastic syndromes (MDS) often require regular transfusions of red blood cell (RBC) units. These patients frequently become transfusion-dependent over time, which has been shown to be an independent prognostic factor for survival, as it reflects the complications deriving from chronic anaemia, infections, or bleeding[1-4]. In a recent expert-panel consensus, an average transfusion volume of two RBC units per month (1.98±0.08 U/month) was considered to be the most appropriate parameter to define a patient as transfusion-dependent[5].

Iron overload develops when excess iron from repeated RBC transfusions is deposited in tissues and organs such as the liver, pancreas, heart, bone marrow, joints and endocrine glands, leading to organ injury and dysfunction. Complications arising from accumulation of iron in these organs include cirrhosis, diabetes, heart failure, arthritis, and an increased risk of infections[6,7]. Previous studies conducted in Spain showed that approximately 9% of apparently healthy subjects have iron overload; however, this incidence increased to 75% in patients with MDS and transfusion dependency[8,9].

In patients who developed iron overload, survival was significantly affected, thereby adding to the impact that transfusion dependency already had on overall survival[6,10,11].

In order to avoid the development of iron overload in frequently transfused patients, the number of RBC units transfused, serum ferritin levels and iron liver concentration must be strictly monitored. The most widely used indirect method to estimate the degree of iron overload and monitor its progression is the measurement of serum ferritin levels. This is an inexpensive, widely available, non-invasive method

that provides a reliable estimate of the liver iron concentration. Although the predictive ability of this test may be affected by inflammation, metastatic disease and chronic diseases, this limitation is usually overcome by repeated measurements over a long period of time[12,13].

Available disease-specific consensus documents and practice guidelines generally agree that iron-chelation therapy should be considered in all patients requiring chronic RBC transfusions, particularly if they have been transfused with more than 10-20 units of packed RBC, and if serum ferritin levels exceed 1,000 ng/mL[14-19].

The purpose of this study was to describe the clinical characteristics of patients with transfusion dependency in Spain under normal clinical practice conditions, in order to obtain a general overview of the current standard of care regarding the diagnosis and management of iron overload. This information will allow us to draw attention to those areas which it would be useful to improve.

Materials and methods

Study design

This was a multicentre, cross-sectional, observational study conducted from November 2008 to December 2009 in 41 Spanish hospitals and day-care centres. To participate, institutions had to have a transfusion service dependent on the hospital's blood bank.

The study was performed according to the principles of the Declaration of Helsinki of 1964, and to standard operating procedures ensuring compliance with Good Clinical Practice Guidelines. The study protocol was approved by the Clinical Research Ethics Committee of the *Hospital Universitari de Tarragona Joan XXIII*, and by the Spanish Agency for Medicinal Products and Medical Devices (AEMPS Registration N : 103123/RG 225826 of November 12, 2008). Written informed consent to participation in the study was obtained from all patients before inclusion.

Study population

Patients aged 18 years or older, with evidence of transfusion dependency due to any underlying condition, undergoing transfusion of RBC during the study's inclusion period, who had received their first transfusion after January 2007, and who had received at least 10 units of packed RBC at the time of inclusion, were eligible for the study. We decided to use transfusion of 10 units of RBC as the threshold for selecting patients because it is widely accepted that iron overload and consequently iron toxicity almost invariably develops when 10-20 consecutive units of RBC have been transfused[20]. Patients who had received multiple transfusions as a result of acute anaemia caused by surgery, trauma or other causes, and patients with any condition or status that in the investigator's opinion advised against participation in the study, were excluded.

Study procedures

Patients visiting the hospital for RBC transfusion were recruited for the study after they had given informed consent and it had been verified that they met the eligibility criteria. Data on demographics, past medical history, underlying conditions of transfusion dependency, transfusion history, ferritin levels and treatment of iron overload were recorded in a Case Report Form. The date of determination of the ferritin level was also recorded. With regards to transfusion history, time elapsed from the first transfusion of RBC units until inclusion in the study (i.e. time of transfusion dependency), time elapsed between the diagnosis of the underlying condition until the first transfusion, as well as the time elapsed between the last two transfusions (i.e. transfusion rate) were recorded. Other data recorded included the number of RBC units transfused until the date of inclusion in the study, and the number of RBC units transfused in the year prior to inclusion in the study.

Statistical analysis

Qualitative variables are described as absolute frequencies and percentages. Quantitative variables are described using the mean, the median, standard deviation and minimum and maximum values. Frequency distributions of qualitative variables were compared using the χ^2 test, and quantitative variables were compared with Student's t test, ANOVA or the Mann-Whitney test. The level of statistical significance was set at $P=0.05$. All statistical analyses were performed using Statistical Analysis Software version 9.1.3.

Results

Patients' characteristics

Between November 2008 and December 2009, a total of 670 patients with transfusion dependency were eligible and enrolled in the study. Of these, 28 (4%) patients were excluded because their first transfusion was not received after January 2007, 10 (2%) because they had not received at least 10 RBC units at the time of inclusion, and one (0.1%) because key data for the study were missing.

Our series comprised 631 patients (355 men and 267 women) with a mean age of 65±17 years. The mean time from diagnosis of the underlying condition to study entry was 2±3 years. The most frequent underlying condition that required chronic RBC transfusion was a haematological disease (92% of patients; Table I). Among these, MDS (36%) and acute myeloid leukaemia (29%) were the most frequent conditions. Additionally, there were 15% of patients

with underlying non-haematological diseases. The most frequent comorbidities present in these patients were cardiovascular diseases (n =154, 24%), followed by urogenital disorders (n =74, 12%) and endocrine diseases (n =64, 10%).

Transfusion history and management of iron overload

Table II shows the transfusion history of the patients. Of note, patients had received a mean of 30±26 RBC units and 59% of patients had received ≥20 RBC units at the time of inclusion in the study.

Table III shows the management of iron overload in the patients included in the study. Serum ferritin levels were known for 528 (84%) patients. The measurement of serum ferritin levels was made before the start of the study in 116 (19%) patients, and during the study period in 412 (65%) patients. There were 307 (58%) patients with serum ferritin levels ≥1,000 ng/mL. However, only 89 (14%) patients were receiving chelation therapy (Table III).

Table I - Underlying conditions necessitating chronic RBC transfusion in 631 patients.

	N.	%
Type of underlying condition		
Haematological condition	533	85
Non-haematological condition	45	7
Both haematological and non-haematological condition	53	8
Description of haematological conditions*	586	92
Myelodysplastic syndromes	226	36
Acute myeloid leukaemia	182	29
Aplastic anaemia	40	6
Chronic myeloproliferative disorders	38	6
Non-Hodgkin's lymphoma	34	5
Haematopoietic stem cell transplantation	32	5
Multiple myeloma	31	5
Other	66	10
Description of non-haematological conditions*	98	15
Solid tumours	42	7
Chronic bleeding	27	4
Renal diseases	27	4
Other	14	2

*Values do not reflect the total number of patients because a patient could have had more than one underlying condition/disease.

Table II - Transfusion history.

End-point	
Time from diagnosis to first transfusion of RBC units (months), n =559	
Mean (SD)	13 (29)
Time of transfusion dependency (months), n =601	
Mean (SD)	10 (8)
Transfusion rate (days), n =602	
Mean (SD)	26 (44)
Number of RBC units transfused to date, n =631	
Mean (SD)	30 (26)
Patients transfused with ≥20 RBC units	374-59%
Patients transfused with <20 RBC units	257-41%
Number of RBC units transfused in the last year, n =616	
Mean (SD)	18 (18)

RBC: red blood cells; SD: standard deviation.

Table III - Management of iron overload.

End-point	N.	%
N. of patients with ferritin level measurements, n =528		
Measured before the start of the study	116	22
Measured after the start of the study	412	78
Ferritin level at study inclusion (ng/mL), n =528		
Mean ± SD	1,570±1,557	
N. of patients with ferritin levels ≥1,000 ng/mL	307	58
N. of patients with ferritin levels <1,000 ng/mL	221	42
N. of patients on chelation therapy, n =618	89	14
Indications for chelation therapy, n =89*		
High SF/TSI	78	88
Transfusion of PRBC units	49	55
Other	3	3
Indications for not receiving chelation therapy, n =529*		
Unknown	178	34
Normal SF/TSI	146	28
Comorbidity	83	16
Other	81	15
Advanced age	61	12
Chelating agent prescribed, n =82		
Deferasirox	73	89
Deferoxamine	8	10
Deferiprone	1	1

*Values do not reflect the total number of patients because a patient could have had more than one indication/reason. PRBC: packed red blood cells; RBC: red blood cells; SD: standard deviation; SF: serum ferritin; TSI: transferrin saturation index.

Discussion

We describe a group of patients dependent on transfusions, mainly because of haematological disease, who had received a large number of RBC units. Despite this, and in relation to iron overload management, serum ferritin levels before starting this study were available for only 18% of patients, and chelation therapy was started in 14% of patients.

As expected, our series included a high number of patients with haematological disease such as MDS and acute myeloid leukaemia. Iron overload should be monitored in patients with MDS because the onset of the harmful effects of iron overload on health can be prevented with a timely diagnosis and start of chelation therapy. However, in the present study we observed that ferritin levels were available for only 18% of patients, but that this value increased to 84% after the start of the study. This is an important finding because different societies and organizations recommend screening for iron overload using the number of RBC units transfused, ferritin levels, or both. The Myelodysplastic Syndromes Foundation states that daily chelation therapy should be initiated when transfusion requirements reach ≥2 units of RBC per month and persist at this level for more than 1 year or when ferritin levels are ≥1,000 ng/mL[17]. Guidelines from the Spanish Association of Haematology and Haemotherapy, the Spanish Society of Thrombosis and Haemostasis and the Italian Society of Haematology recommend starting chelation therapy in patients with MDS and transfusion-dependent anaemia, and when ferritin levels are >1,000 ng/mL[21,22]. The National Comprehensive Cancer Network recommends starting treatment in patients with MDS who have received or are anticipated to receive ≥20 units of RBC, or when serum ferritin levels are >2,500 ng/mL[23]. Regarding thalassaemic children, the Italian Society of Haematology states that iron chelation should be started in regularly transfused children after they have received more than 10 units of blood, or when serum ferritin levels are over 1,000 ng/mL[19].

Serum ferritin level is the most useful parameter to evaluate the degree of iron burden. Because serum ferritin levels tend to correlate well with liver iron concentration[24], most guidelines agree that a level ≥1,000 ng/mL is indicative of iron overload, and recommend starting chelation therapy in patients with such levels[17,19,21]. However, despite the fact that 58% of patients in our study had serum ferritin levels ≥1,000 ng/mL, only 14% were receiving chelation therapy. Interestingly, in 178 patients the reasons for withholding chelation therapy were not known.

All guidelines agree that serum ferritin levels should be measured every 1 to 3 months in patients with transfusion dependency in order to obtain baseline values for initiating chelation therapy and to monitor the efficacy of the treatment. In this study, we observed that only 18% of patients had ferritin measurements available before starting the study. In most of the patients who had ferritin levels available for analysis, the measurement had been done during the study period (65%). This result points towards a discrepancy between what is recommended by current guidelines and the standard of care exercised by our health care providers. Physicians should be aware of the consequences of not monitoring ferritin levels early and routinely in patients considered to be transfusion dependent.

Discrepancies in the standard of care regarding monitoring of iron overload and related complications was reported in a similar study in transfusion-dependent patients with sickle cell disease at 31 haematology clinics in the USA, Canada and the United Kingdom[25]. Observational studies of this sort are needed to draw the attention of societies and organisations to the fact that a standardisation of treatment recommendations is warranted. In the meantime, physicians must be aware of the differences in practice guidelines, and adhere to local recommendations if available, or to those that best fit the characteristics of the population, in order to avoid delays in the diagnosis and treatment of iron overload in transfusion-dependent patients.

As stated before, another easy way to suspect iron overload is when a patient has received at least 10-20 RBC units[17]. With regards to this, we are working on the development of a software tool, compatible with blood bank computer systems, to give an alert when a chronically transfused patient has received ≥20 RBC units for >5 months. In this situation, the person responsible for the blood transfusion service communicates this information to the physician who is taking care of the patient[26]. We believe this information will help physicians to be aware of the possibility of iron overload and to carry out more efficient monitoring of ferritin levels.

In conclusion, we have reported the results of an observational study of a group of patients who had received a large number of RBC transfusions and had iron overload. With regards to monitoring iron overload, we found a discrepancy between what is recommended by current guidelines and the standard of care exercised by our health care providers. Physicians should be aware of the consequences of not monitoring ferritin levels early and routinely in patients considered to be transfusion-dependent.

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Conflict of interest disclosure

The Authors declare that they have no conflicts of interest relevant to the manuscript submitted to the journal. All Authors had full control of all primary data and agree to allow the journal to review their data if requested.

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