



HAL
open science

Iron overload and chelation therapy in patients with low-risk myelodysplastic syndromes with transfusion requirements

Angel F. Remacha, Beatriz Arrizabalaga, Consuelo Cañizo, Guillermo Sanz, Ana Villegas

► **To cite this version:**

Angel F. Remacha, Beatriz Arrizabalaga, Consuelo Cañizo, Guillermo Sanz, Ana Villegas. Iron overload and chelation therapy in patients with low-risk myelodysplastic syndromes with transfusion requirements. *Annals of Hematology*, 2009, 89 (2), pp.147-154. 10.1007/s00277-009-0794-7. hal-00535080

HAL Id: hal-00535080

<https://hal.science/hal-00535080>

Submitted on 11 Nov 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Iron overload and chelation therapy in patients with low-risk myelodysplastic syndromes with transfusion requirements

Angel F. Remacha · Beatriz Arrizabalaga ·
Consuelo Del Cañizo · Guillermo Sanz · Ana Villegas

Received: 18 May 2009 / Accepted: 9 July 2009 / Published online: 19 August 2009
© Springer-Verlag 2009

Abstract The main objective of the study was to analyze the incidence of iron overload (IO) and its management in transfusion-dependent patients with low-risk myelodysplastic syndrome (MDS) before the license of deferasirox. This observational, cross-sectional, and multicenter study was conducted from January to May 2007 in 81 Spanish hospitals. Eligible patients had a low or intermediate-1 risk score and had to have received at least ten units of packed red blood cell (PRBC). Of the 549 patients analyzed, 75% had received more than 20 PRBC units since diagnosis; 14% had IO at diagnosis and 58% at last follow-up. Thirty-eight percent of patients received chelation therapy; of those, 92% were treated with desferrioxamine. Ferritin levels at the start of chelation therapy were higher than 1,000 $\mu\text{g/L}$ in 76% and over 2,500 $\mu\text{g/L}$ in 24% of patients. Of the 202 patients who received some form of chelation therapy, ferritin levels

increased from a mean \pm SD of 1,986 \pm 1,398 to 2,480 \pm 1,648 $\mu\text{g/L}$ at last follow-up in 86% ($p<0.001$). In the remaining 29 patients treated with a minimally effective therapy, ferritin levels did not increase. Of these, only 11 patients received such therapy lasting more than 12 months. In conclusion, most low-risk transfusion-dependent MDS patients develop IO, but only a minority receives a minimally effective and timely iron chelation therapy.

Keywords MDS · Chelation · Iron · Overload · DFO · Deferasirox

Introduction

Myelodysplastic syndromes (MDS) are a group of clonal disorders characterized by peripheral blood cytopenias, morphologic dysplasia secondary to bone marrow dysfunction, and genetic instability with enhanced risk of developing acute myeloid leukemia [1]. MDS can affect people of any age [2], although the elderly are particularly vulnerable. Their incidence has been estimated at 3.3 cases per 100,000 people per year, but it may increase to 15–50 cases per 100,000 people per year in patients over the age of 70 years [3].

At diagnosis, 80% to 85% of the patients with MDS are anemic; around 40% show neutropenia and 30% thrombopenia [1, 4]. Despite the recent progresses in treatment, the standard of care in the community for MDS is best supportive care, with most patients requiring chronic transfusions of packed red blood cell (PRBC) to alleviate symptomatic anemia. One of the major consequences of transfusion therapy is iron overload (IO). Over time, IO evolves into overt organopathy, such as hepatopathy and cardiomyopathy, with the consequent increase in mortality

A. F. Remacha (✉)
Hematology Department, Centro Hospitalario de Toledo,
Avenida Barber, 30.,
45004 Toledo, Spain
e-mail: aremacha@sescam.jccm.es

B. Arrizabalaga
Hospital de Cruces,
Barakaldo, Spain

C. Del Cañizo
Hospital Universitario de Salamanca,
Salamanca, Spain

G. Sanz
Hospital La Fe,
Valencia, Spain

A. Villegas
Hospital Clínico San Carlos,
Madrid, Spain

unless an adequate timely and individualized chelation therapy is established [5–8]. It has been shown that, in patients with refractory anemia, transfusion dependency is associated with shorter survival rates, higher risk of leukemic progression, and a higher mortality related to heart failure and secondary IO [9, 10]. In this regard, a previous study carried out by Malcovati et al. [10] showed that the development of secondary IO significantly affected overall survival and demonstrated a clear relationship between the number of PRBC units transfused and the patient's prognosis. Increased mortality due to secondary IO results from non-transferrin-bound iron-induced production of highly reactive oxygen species, which leads to a significant and extensive liver, heart, and endocrine organ injury, as well as a greater propensity for infection [11].

In order to achieve safe iron levels in tissues and plasma, published guidelines recommend the use of chelation therapy for the management of MDS patients [12, 13]. According to these guidelines, for patients to be considered candidates for iron chelation therapy, they must be transfusion dependent, have a life expectancy of more than 1 year, and have a stable or increasing serum ferritin level above 1,000 $\mu\text{g/L}$.

For many years, the outstanding “gold standard” for iron chelation in MDS has been desferrioxamine (DFO), but the inconvenience of prolonged subcutaneous infusion is believed to be a major handicap for the administration of this drug. The magnitude of this problem remains unknown, as no studies specifically addressing the management of IO in MDS patients have been published. Information on this issue is particularly important in the light of the recent availability of a new oral iron chelator.

The main objectives of this study were to describe the IO and chelation therapy patterns in a large series of patients with low-risk MDS who require PRBC transfusion support and to assess the efficacy and limitations of iron chelation therapies available for MDS patients before the licensing of deferasirox. The results obtained might be used in the future as a useful comparison resource to address the impact of this new oral iron chelator in the clinical practice.

Patients and methods

Study design

This was an observational, cross-sectional, noninterventional, and multicenter study conducted over 5 months (January to May 2007) in 81 hospitals throughout Spain that represent 42% of the hospitals belonging to the Spanish National Health Care System. The study was approved by the Institutional Review Board, and it was conducted in accordance with the Helsinki Declaration of the World

Medical Association amended in 1975 and subsequent revisions. All patients provided a written informed consent. Data were collected in appropriate case report forms, and confidentiality was maintained across the study.

Study procedures

Eligibility criteria were: (1) MDS patients with a low or intermediate-1 International Prognostic Scoring System (IPSS) risk score or a low Spanish Prognostic Index (SPI) risk score, in those patients in whom cytogenetic studies were not available, (2) patients who had received at least ten PRBC units, and (3) patients who attended a medical consultation in a period of 5 months between January and May 2007.

Variables included in the analysis were: (1) demographics (age and gender), (2) clinical data at diagnosis (date of diagnosis, symptoms, comorbidities, and concomitant diseases), (3) hematological parameters at presentation (hemoglobin [Hb] level, absolute neutrophil and platelet counts, and proportion of blast cells in bone marrow), (4) cytogenetics (conventional karyotype and fluorescence in situ hybridization [FISH], if available), (5) morphological classification (by IPSS and SPI), (6) treatment received for MDS (erythropoietin, granulocyte colony-stimulating factor, lenalidomide, thalidomide, chemotherapy, and others), (7) data about PRBC transfusion requirements (date of first PRBC transfusion and number of PRBC units administered from diagnosis and during the last 12 months), (8) serum ferritin levels (at diagnosis, at the start of iron chelation therapy, and at last assessment), and (9) data about iron chelation therapy (date of first and last administration of an iron chelating agent, drug/s, dose/s, schedule/s and route/s used, duration of chelation with every drug used, and reason for discontinuation or change in prescription).

Definitions

IO was defined as serum ferritin levels above 1,000 $\mu\text{g/L}$. Minimally effective chelation treatment with DFO was defined as having received at least a daily dose of 25 mg/kg or 2 g for at least 3 days a week.

Statistical analysis

Continuous variables were described using mean, median, standard deviation, and minimum and maximum values and were compared using analysis of variance (ANOVA). Frequency distributions of discrete variables were compared using chi-squared test or Fisher's exact test as appropriate. Significance level was set at $p < 0.05$. Statistical analysis was performed using the statistical software program SPSS® version 13.0

Results

Baseline patient characteristics

Of the 626 MDS patients initially selected to participate in this study, 549 (88%) were finally analyzed. Sixty-two (10.0%) patients were excluded because they did not meet the protocol pre-established eligibility criteria, nine (1.0%) because they had serum ferritin levels lower than 50 $\mu\text{g/L}$, which could indicate a possible concomitant iron deficiency anemia, four (0.6%) due to the lack of clinical data, and two (0.3%) because the bone marrow study was inadequate to support the diagnosis of MDS.

The main characteristics of the 549 patients included in the study are shown in Table 1. Median age was 77 years (range 31–97) with half of the patients (51%) belonging to the 66–79 age group. The median Hb level at diagnosis was 90 g/L (35–138 g/L). Twenty-five percent of the patients had an Hb level lower than 80 g/L. Neutropenia and

thrombocytopenia were observed at diagnosis in 27% and 11% of the patients, respectively. Successful bone marrow karyotyping was available in 67% of the patients. FISH was carried out in 12% of the patients. Most patients (66%) reported fatigue as the main initial complaint. A high proportion of patients had a previous history of heart disease (30%), vascular disease (29%), and/or endocrine, nutritional, or metabolic disorders (28%).

Tables 2, 3, 4, and 5 show the characteristics of the patients according to the WHO and FAB classifications, as well as IPSS and SPI prognostic indexes. The most frequent morphological diagnosis was refractory anemia with ringed sideroblasts (RARS) followed by refractory anemia (RA), which were observed in 34% and 24% of the patients, respectively. According to the IPSS, 62% and 38% of the patients had low and intermediate-1 risk, respectively. The treatments received for the management of MDS, including growth factors, chemotherapy, and other drugs, are shown in Table 6.

Table 1 Baseline patient characteristics

Characteristic	Number	Percentage
Age (years), $n=540$		
Median (range)		77 (31–97)
$\leq 65/66\text{--}79/>80$	75/276/189	14/51/35
Gender, $n=545$		
Male/female	298/247	55/45
Hemoglobin (g/L), $n=545$		
Median (range)		90 (35–138)
$<80/80\text{--}100/>100$	136/332/77	25/61/14
Neutrophils ($\times 10^9$ per liter), $n=528$		
Median (range)		2.8 (0.2–21.0)
$<1.8/>1.8$	141/387	27/73
Platelets ($\times 10^9$ per liter), $n=549$		
Median (range)		215 (7–855)
$<100/>100$	60/489	11/89
Blasts (%), $n=549$		
Median (range)		1 (0–10)
$<5/5\text{--}10$	511/38	93/7
Bone marrow karyotype, $n=369$	369	67
Prognosis according to karyotype		
Bad/intermediate/good	1/41/327	1/11/88
Symptoms at diagnosis, $n=549$		
Fatigue	361	66
Appetite and weight loss	104	19
Bleeding	29	5
Fever	21	4
Exertional dyspnea	12	2
Time from diagnosis (years), $n=517$		
$<1/1\text{--}3/3\text{--}5/>5$	38/245/98/136	7/47/20/26
Median (\pm SD)		3 (\pm 4)

Bad prognosis: 7/del(7q) and complex karyotypes; intermediate prognosis: +8 and other cytogenetic abnormalities; good prognosis: normal karyotype, del(5q), del(20q), and -Y karyotypes

Table 2 MDS classification according to WHO index

Type of MDS	Total (<i>n</i> =549)		≤65 (<i>n</i> =75)		66–79 (<i>n</i> =279)		≥80 (<i>n</i> =195)	
	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
RARS	188	34	13	17	96	34	79	41
RA	133	24	16	21	69	25	48	25
RCMD	69	13	11	15	40	14	18	9
MDS with isolated del(5q)	54	10	18	24	20	7	16	8
RCMD with RS	44	8	9	12	20	7	15	8
RA with excess blasts, type 1	25	5	2	3	16	6	7	3
MDS, unclassifiable	36	6	6	8	18	7	12	6

MDS myelodysplastic syndrome, WHO World Health Organization, RA refractory anemia, RARS refractory anemia with ringed sideroblasts, RCMD refractory cytopenias with multilineage dysplasia, RS ringed sideroblasts

Transfusions

The median time elapsed from diagnosis to the first transfusion of PRBC was 2 years (range 0–18 years). Out of 549 patients, 56 (10%) received their first transfusion within the first year after diagnosis, 153 (28%) during the second year, and 108 (20%) during the third year, and 232 (42%) patients received the first transfusion after more than 3 years had elapsed since diagnosis. The median number of PRBC units transfused since diagnosis was 35 (range 10–454 units) and 22 units during the last year (range 0–120). Thirty-eight percent (196 out of 513) patients had received between 20 and 49 units of PRBC since diagnosis, and 37% (*n*=190) had received more than 50 units. Patients aged 65 years or less had received a significantly higher number of PRBC units in the previous 12 months and since diagnosis than patients aged 80 years or more (*p*<0.05).

Iron overload and chelation treatment

Median serum ferritin level at diagnosis was 408 µg/L (range 120–7,339). Sixty-eight (14%) patients had serum ferritin levels between 1,000 and 2,499 µg/L, and nine (2%) patients had serum ferritin levels greater than 2,500 µg/L.

Overall, 202 out of 536 (38%) patients with low-risk MDS received chelation therapy. Of these, 154 (76%) patients had baseline ferritin levels greater than 1,000 µg/L

and 48 (24%) patients had ferritin levels greater than 2,500 µg/L. The average serum ferritin level at the beginning of treatment was 1,986±1,398 µg/L. Time from diagnosis to the start of chelation therapy was after (a) five or more years in 55% of patients, (b) 2 to 5 years in 34% of patients, and (c) less than 2 years in 21% of patients. In patients who had developed IO (14%), 92% of those aged 65 years or less and with serum ferritin levels greater than 1,000 µg/L received DFO therapy; this percentage decreased to 52% in patients with ages between 66 and 79 years and to 32% in patients aged 80 years or more.

Of the 202 patients who received chelation therapy, DFO was used in 93% (*n*=188) of the patients. However, only 29 (14%) patients received a minimally effective dose of DFO and only in 11 patients was DFO administered for more than 12 months.

Serum ferritin levels in the 334 (62%) patients who did not receive any type of chelation therapy significantly increased from 512±615 µg/L at diagnosis to 1,633±1,401 µg/L at last follow-up (*p*<0.001). The last ferritin level recorded in this group showed that 152 (46%) of these patients had already developed IO. Of the 202 patients who received some kind of chelation therapy, either minimally effective or not, serum ferritin levels significantly increased from 1,986±1,398 µg/L at the start of treatment to 2,481±1,648 at the last assessment (*p*=0.001). However, in patients who received a minimally effective chelation therapy (*n*=29), serum ferritin levels did not increase over time (from 2,037±1,304 µg/L at the start of treatment to 1,798±1,459 µg/L at the last follow-up; Fig. 1). No significant differences were observed regarding changes in serum ferritin levels and patient's age, type of MDS anemia, or use of chelation therapy.

Table 3 MDS classification according to FAB index

Type of MDS, <i>n</i> =505	Number	Percent
RA	231	46
RARS	231	46
RA with excess blast	27	5
CMML	16	3

MDS myelodysplastic syndrome, FAB French–American–British, RA refractory anemia, RARS refractory anemia with ringed sideroblasts, CMML chronic myelomonocytic leukemia

Discussion

The results obtained in the current study show that, in the year 2007, when DFO was the only drug licensed for iron chelation in MDS, only a minority of patients with low-risk

Table 4 MDS severity at diagnosis according to IPSS prognostic index

	Total (n=369)		Prognosis according to karyotype						
	n	%	Good (n=327)		Intermediate (n=41)		Bad (n=1)		
			n	%	n	%	n	%	
Low (score=0); intermediate-1 (score=0.5–1); intermediate-2 (score=1.5–2.0), high (score≥2.0)									
Low	229	62	219	67	8	20	0	0	0
Intermediate-1	140	38	108	33	33	80	1	100	
Intermediate-2	0	0	0	0	0	0	0	0	0
High	0	0	0	0	0	0	0	0	0

IPSS International Prognostic Scoring System

MDS and IO received iron chelation therapy. Furthermore, in many patients, iron chelation treatment was started later than what is currently recommended [10], and, in most cases, the dosage used was not considered minimally effective to achieve an adequate control of IO. According to the group of Malcovati et al. [7, 10], ferritin levels of 1,000 µg/L are reached when patients are transfused a median of 21 PRBC units. They have also shown that patient survival is adversely affected as transfusions increase due to a greater risk of developing IO and secondary hemochromatosis [7, 10]. In a retrospective analysis of 46 MDS patients who had received more than 50 units of PRBC during the course of the disease, 20 patients developed heart failure; 11 suffered from hepatopathy; five developed diabetes mellitus, and 14 patients died from refractory congestive heart failure related with IO [14]. Besides IO-related clinical complications, a number of different factors may contribute to the negative effect of transfusion dependency on survival, including more severe disease (higher risk of leukemic progression) and more severe anemia (higher mortality due to heart failure) [7, 9, 15]. Based on these facts, during the recent years, iron chelation is being recommended for low-risk MDS patients with transfusion requirements [13, 16]. Given that the majority of patients in this study were classified as having RARS, RA, or refractory cytopenias with multilineage dysplasia and had received a median of 22 PRBC units during the last year, they would potentially benefit from iron chelation therapy according to the current guidelines [16].

Table 5 MDS severity at diagnosis according to SPI prognostic index

n=549	Number	Percent
Low	478	87
Intermediate	71	13
High	0	0

Low (score=0.0–1.0); intermediate (score=2.0–3.0); high (score=4.0–5.0)

SPI Spanish Prognostic Index

One of the most significant results of this study was that only 37% of patients were treated with chelation therapy, despite the fact that the majority of them had clinical indications for receiving it. This underscores the importance of taking into consideration not only ferritin levels but also the number PRBC units transfused. Several reasons might have influenced the physicians' decision to delay or to avoid chelation therapy and include the high rate of dropouts due to DFO intolerance, a potential lack of awareness of the benefits of a timely chelation therapy, and the patient's age. In this regard, in patients with ferritin levels greater than 1,000 µg/L, only 32% of patients aged ≥80 years received chelation with DFO versus 92% of patients aged ≤65 years. These results show that chelation therapy was started, in spite of DFO intolerance, in the youngest MDS patients with IO. Age is an important factor to take into account when making the decision to start chelation therapy since MDS patients who have a short

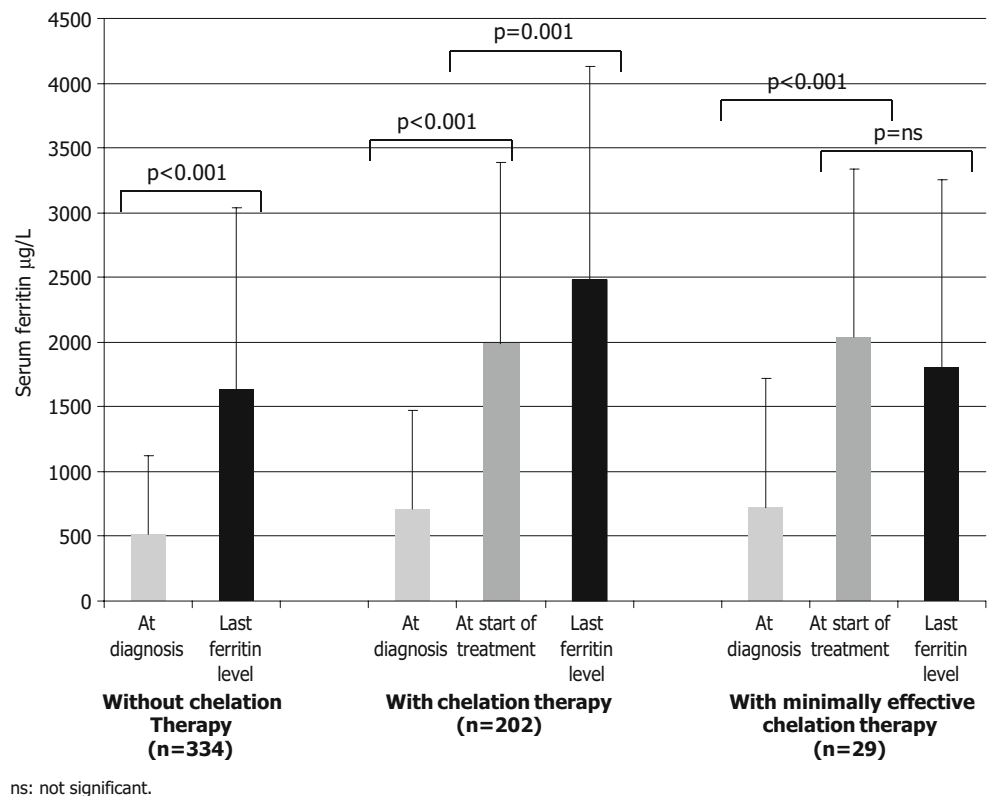
Table 6 Treatments received by patients with MDS (n=549)

Type of treatment	Number	Percent
Growth factors, n=390		
EPO	265	68
EPO + GCSF	125	32
Chemotherapy, n=27 ^a		
Hydroxyurea	19	70
Cytarabine	3	11
Etoposide	2	7
Combination chemotherapy	2	7
Other drugs, n=104 ^a		
Lenalidomide	36	35
Corticosteroids	30	29
Vitamin B	23	22
Cyclosporine	16	15
Thalidomide	9	9
Antithymocyte globulin	5	5

GCSF growth colony-stimulating factor

^a One or more than one

Fig. 1 Impact of chelation therapy on serum ferritin levels ($\mu\text{g/L}$). *ns* not significant



expected survival will probably not benefit from such treatment [17].

The fact that, until recently, iron chelation treatment recommendations in MDS were based on limited data further complicates the picture (evidence grade B, level III) [18]. Nowadays, several comparative studies have shown that mortality is higher in heavily iron-overloaded patients [19, 20] and that chelation treatment seems to improve survival in MDS patients [16, 21]. The guidelines published to date regarding IO treatment agree that iron chelation therapy is indicated in patients with a ferritin level of 1,000 $\mu\text{g/L}$ or more and/or who have received a transfusion of two units per month of PRBC for at least 1 year [16, 21]. In contrast, iron chelation should not be offered to patients with an anticipated survival of less than 1 year [16]. From our results, it seems that iron chelation therapy was started too late since 76% of the patients had ferritin levels above 1,000 $\mu\text{g/L}$ and 24% had ferritin levels above 2,500 $\mu\text{g/L}$ at the start of chelation therapy. In addition, chelation therapy was administered only to half of the MDS patients when five or more years had elapsed since diagnosis.

Another interesting observation was that only a minority of the patients exposed to chelation therapy received a minimally effective chelation treatment with DFO. This result might reflect the low compliance rate in MDS patients treated with DFO, which is probably related to its administration schedule, as it has been

previously described in a Spanish prospective study [22]. Also, our results showed that ferritin levels increased in patients who received inadequate chelation therapy. In contrast, in patients who received a minimally effective dose of DFO, ferritin levels were stabilized and did not increase in spite of the transfusions received. These results reinforce the assumption that chelation therapy must be included in guidelines designed for the treatment of MDS patients.

The results of this observational study should be interpreted in the light of potential limitations, which reside mainly in the lack of randomization and blindness inherent to the study's design. Nevertheless, this study has shown that, despite the fact that there is scientific evidence to support chelation therapy in MDS patients with transfusion requirements, chelation is not as widely used as it should, except perhaps in the youngest population, probably due, in part, to the fact that, at the time of this study, DFO was the only iron chelator licensed for use in patients with MDS who are transfusion dependent. Also, single measurements of ferritin levels have limitations and should not be the only factor to consider when assessing IO and chelation therapy efficacy [23]. However, repeated serum ferritin level measurements are currently the most widely used monitoring technique, partly due to its wide availability, noninvasive nature, and inexpensiveness and due to the fact that there is no optimal test for this purpose [12, 24].

In summary, in this group of MDS patients with transfusion requirements, it seems that patients with IO were undertreated, as chelation therapy was started late and was not administered rigorously enough. Nowadays, MDS patients live longer and receive more PRBC transfusions, and, consequently, physicians should be aware of the potential organ damage related to iron accumulation in order to prevent it or treat it.

Acknowledgements The authors are grateful to all the patients who participated in this study and the 114 hematologists who contributed to the data collection; to HealthCo (Madrid, Spain) for assistance with preparation of the manuscript and to Novartis Spain for funding the project.

Appendix

Participating physicians and affiliations are, in alphabetical order, as follows: Aguado Bueno, Hospital de la Princesa (Madrid), Allegue Vilaso, Complejo Hospitalario de Pontevedra (Pontevedra), Almagro Sánchez de Puerta, Hospital Virgen de las Nieves (Granada), Alonso Rosa, Hospital Virgen del Rocío (Sevilla), Altes Hernández, Hospital Espíritu Santo (Barcelona), Álvarez Rivas, Hospital Reina Sofía (Córdoba), Andreu Lapiedra, Hospital Universitario Dr. Peset (Valencia), Arrizabalaga Amuchastegui, Hospital de Cruces (Vizcaya), Atutxa Aresti, Hospital Comarcal de Galdácano (Vizcaya), Bailén García, Hospital Carlos Haya (Málaga), Barbón Fernández, Hospital de León (León), Bargay Llonart, Hospital Sont Llatzer (Balears), Beltrán de Heredia, Hospital de Basurto (Vizcaya), Benavente Cuesta, Hospital Clínico San Carlos (Madrid), Bendaña López (Hospital Clínico Universitario Santiago Compostela (La Coruña), Bermejo Estevan, Hospital Sagrado Corazón (Barcelona), Bernal del Castillo, Hospital Universitario Central de Asturias (Asturias), Biedma López, Hospital San Juan de la Cruz (Jaén), Blanchard Rodríguez, Hospital Ramón y Cajal (Madrid), Bombin Canal, Hospital Ramón y Cajal (Madrid), Bosch Llobet, Hospital de Mataró (Barcelona), Calavia Lacarra, Hospital San Millán (La Rioja), Cano Luis, Complejo Hospitalario 'La Mancha-Centro' Ciudad Real), Carbonell Ramón, Consorcio Hospital General (Valencia), Carrascosa Vallejo, Hospital Comarcal de Galdácano (Vizcaya), Casaño Sánchez, Hospital Reina Sofía (Córdoba), Castro Mouzo, Complejo Hospitalario de Vigo-Hospital Xeral-Cies (Pontevedra), Cladera Serra, Hospital Sont Llatzer (Balears), Clavero Ferrer, Hospital Torrecárdenas (Almería), Clavero Sánchez Hospital de Motril (Granada), De la Rubia Hospital Universitario La Fe (Valencia), De Paz Arias, Hospital Universitario La Paz (Madrid), Del Campo Rincón Complejo Hospitalario 'La Mancha-Centro' (Ciudad Real), Del Cañizo Fernández Roldán, Hospital C.U. de Salamanca (Salamanca), Del Castillo Rueda, Hospital Gregorio Marañón (Madrid),

Durán Nieto, Hospital Ciudad de Jaén (Jaén), Duran Pastor, Hospital Son Dureta (Balears), Estany Raluy, Hospital Mutua Terrassa (Barcelona), Esteban Muñoz, Hospital Ciudad de Jaén (Granada), Fernández de la Mata, Hospital Infanta Margarita—Cabra (Córdoba), Fernández Lago, Complejo Hospitalario Juan Canalejo (La Coruña), Figueredo Manrique, Hospital Virgen de la Macarena (Sevilla), Font Ferré, Hospital Tortosa Verge de la Cinta (Tarragona), Franco Osorio, Hospital Punta de Europa (Cádiz), Funes Vera, Hospital Santa Maria del Rosell (Murcia), Gallardo Giralt, Instituto Catalán de Oncología (ICO; Barcelona), García Delgado, Hospital Clínico Universitario de Málaga (Málaga), García Frade, Hospital Rio Hortega (Valladolid), García Hernández, Hospital General Universitario de Alicante (Alicante), García Menoyo, Hospital de Basurto (Vizcaya), García Pintos, Consorcio Sanitario de Terrassa (Barcelona), Giraldo Castellanos, Hospital Miguel Servet (Zaragoza), Gómez García de Soria, Hospital de la Princesa (Madrid), González González, Hospital Universitario de Canarias (Tenerife), González Navarro, Hospital Nuestra Señora de la Salud (Granada), Gonzalez Porras, Hospital Clínico Universitario de Salamanca (Salamanca), González Rodríguez, Hospital de Cabueñes (Asturias), Gorosquieta Sánchez, Hospital de Navarra (Navarra), Groiss Buiza, Hospital Infanta Cristina (Badajoz), Guerra Hernando, Hospital Sont Llatzer (Balears), Guzmán Zamudio, Hospital del SAS de Jerez (Cádiz), Hernández Regi, Hospital de Calella (Barcelona), Lemes Castellano, Hospital Dr. Negrín Las Palmas Gran Canaria (Canarias), León Lara, Hospital de Jerez de la Frontera (Cádiz), Llorente Cabrera, Hospital Juan XXIII (Tarragona), López García-Carreño, Hospital Santa Maria del Rosell (Murcia), López Garrido, Hospital Virgen de las Nieves (Granada), López López, Hospital Virgen del Puerto (Cáceres), Macía Virgili, Hospital Universitario Arnau de Vilanova (Lerida), Márquez Navarro, Hospital de Basurto (Vizcaya), Martí Tutusaus, Hospital Mutua Terrassa (Barcelona), Martín Antorán, Hospital Universitario Rio Hortega (Valladolid), Martínez Bilbao, Hospital Comarcal de Galdácano (Vizcaya), Mascaró Riera, Hospital Sont Llatzer (Balears), Menchaca Echevarría, Hospital Xagorritxu de Vitoria (Álava), Montesinos Fernández, Hospital Universitario La Fe (Valencia), Muñoz Muñoz, Hospital Puerta el Mar (Cádiz), Navarro Álvarez, Hospital Virgen de las Nieves (Granada), Ojanguren Bergaz, Hospital Comarcal de Aldácano (Vizcaya), Ojeda Gutiérrez, Clínica Puerta de Hierro (Madrid), Olabarria Santuizun, Hospital de Basurto (Vizcaya), Orriols Bernet, Fundación Manresa Althaia (Barcelona), Ortega Rivas Centro Asistencial de Palencia (Palencia), Ortiz Conde, Hospital Universitario 12 de Octubre (Madrid), Osorio Prendes Hospital Gregorio Marañón (Madrid), Palomera Bernal Hospital Clínico de Zaragoza (Zaragoza), Pascual García, Hospital Príncipe de Asturias-Alcalá de Henares (Madrid), Pedro Olivé, Hospital del

Mar (Barcelona) Pérez Mendiguren Ruiz de Olalla, Hospital General Yagüe (Burgos), Pérez-Pons de la Villa, Hospital Severo Ochoa-Leganés (Madrid), Peris Vidal, Hospital Municipal de Badalona (Barcelona), Plensa Alberca Hospital de Mataró (Barcelona), Prieto Pareja, Fundación Jiménez Díaz (Madrid), Rabasa Garaibar, Hospital San Millán (La Rioja), Ramos Ortega, Hospital de León (León), Remacha Sevilla, Hospital de la Santa Creu i Sant Pau (Barcelona), Requena Vilaplana, Hospital San Juan de la Cruz (Jaén), Ríos Tamayo, Hospital Comarcal Valle de los Pedroches (Córdoba), Rodríguez Fernández, Hospital de Mataró (Barcelona), Rodríguez Rodríguez, Hospital Juan Ramón Jiménez (Huelva), Ruiz Marco, Hospital General de Albacete (Albacete), Sánchez García, Hospital Vall d'Hebron (Barcelona), Sánchez García, Hospital Reina Sofía (Córdoba), Sánchez-Tello de Carranza, Hospital Arnau de Vilanova (Valencia), Sanz Santillana, Hospital Universitario La Fe (Valencia), Solano Ramos, Hospital Ntra. Sra. del Prado-Talavera de la Reina (Toledo), Solano Vercet, Hospital Clínico Universitario de Valencia (Valencia), Soler Campos, Hospital Parc Taulí (Barcelona), Tejedor Gutiérrez, Hospital Santa Maria del Rosell (Murcia), Torres González, Hospital Torrecárdenas (Almería), Uranga Uranga, Hospital Donostia (Guipúzcoa), Urbano Ramos, Hospital Comarcal Valle de los Pedroches (Córdoba), Vela Payan, Hospital de Calella (Barcelona), Verruga Oñate, Hospital San Juan de la Cruz (Jaén), Vicente Folch, Consorcio Sanitario de Terrassa (Barcelona), Vicente García Hospital Universitario Morales Meseguer (Murcia), Villegas Martínez, Complejo Universitario San Carlos (Madrid), Xicoy Cirici, Hospital German Trias i Pujol (Barcelona), Yáñez Sansegundo, Hospital Marqués de Valdecilla (Santander).

References

- Greenberg P, Cox C, LeBeau MM et al (1997) International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 89:2079–2088
- Aul C, Gattermann N, Schneider W (1992) Age-related incidence and other epidemiological aspects of myelodysplastic syndromes. *Br J Haematol* 82:358–367
- Aul C, Germing U, Gattermann N, Minning H (1998) Increasing incidence of myelodysplastic syndromes: real or fictitious? *Leuk Res* 22:93–100
- Steensma DP, Bennett JM (2006) The myelodysplastic syndromes: diagnosis and treatment. *Mayo Clin Proc* 81:104–130
- Modell B, Khan M, Darlison M (2000) Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia Register. *Lancet* 355:2051–2052
- Greenberg PL (2006) Myelodysplastic syndromes: iron overload consequences and current chelating therapies. *J Natl Compr Canc Netw* 4:91–96
- Malcovati L, Della Porta MG, Cazzola M (2006) Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. *Haematologica* 91:1588–1590
- Valent P, Horny HP, Bennett JM et al (2007) Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: consensus statements and report from a working conference. *Leuk Res* 31:727–736
- Malcovati L (2007) Impact of transfusion dependency and secondary iron overload on the survival of patients with myelodysplastic syndromes. *Leuk Res* 31(Suppl 3):S2–S6
- Malcovati L, Porta MG, Pascutto C et al (2005) Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol* 23:7594–7603
- Ozment CP, Turi JL (2009) Iron overload following red blood cell transfusion and its impact on disease severity. *Biochim Biophys Acta* 1790:694–701
- Gattermann N (2008) Overview of guidelines on iron chelation therapy in patients with myelodysplastic syndromes and transfusional iron overload. *Int J Hematol* 88:24–29
- Bennett JM (2008) Consensus statement on iron overload in myelodysplastic syndromes. *Am J Hematol* 83:858–861
- Jaeger M, Aul C, Sohngen D, Germing U, Schneider W (1992) Secondary hemochromatosis in polytransfused patients with myelodysplastic syndromes. *Beitr Infusionsther* 30:464–468
- Sanz G, Nomdedeu B, Such E et al (2008) Independent impact of iron overload and transfusion dependency on survival and leukemic evolution in patients with myelodysplastic syndrome. *ASH Annual Meeting Abstracts* 112:640
- Gattermann N (2007) Guidelines on iron chelation therapy in patients with myelodysplastic syndromes and transfusional iron overload. *Leuk Res* 31(Suppl 3):S10–S15
- Mittelman M, Lugassy G, Merkel D et al (2008) Iron chelation therapy in patients with myelodysplastic syndromes: consensus conference guidelines. *Isr Med Assoc J* 10:374–376
- Takatoku M, Uchiyama T, Okamoto S et al (2007) Retrospective nationwide survey of Japanese patients with transfusion-dependent MDS and aplastic anemia highlights the negative impact of iron overload on morbidity/mortality. *Eur J Haematol* 78:487–494
- Leitch HA, Goodman TA, Wong KK, Vickars LM, Galbraith PF, Leger CS (2006) Improved survival in patients with myelodysplastic syndrome (MDS) receiving iron chelation therapy. *ASH Annual Meeting Abstracts* 108:249
- Rose C, Brechignac S, Vassilief D et al (2007) Positive impact of iron chelation therapy (CT) on survival in regularly transfused MDS patients. A prospective analysis by the GFM. *ASH Annual Meeting Abstracts* 110:249
- Valent P, Krieger O, Stauder R et al (2008) Iron overload in myelodysplastic syndromes (MDS)—diagnosis, management, and response criteria: a proposal of the Austrian MDS platform. *Eur J Clin Invest* 38:143–149
- González FA, Arrizabalaga B, Villegas A et al (2005) Study of deferoxamine in subcutaneous profusion treatment of iron overload in myelodysplastic syndromes. *Med Clin (Barc)* 124:645–647
- Wish JB (2006) Assessing iron status: beyond serum ferritin and transferrin saturation. *Clin J Am Soc Nephrol* 1:S4–S8
- Barton JC (2007) Optimal management strategies for chronic iron overload. *Drugs* 67:685–700