Impact of treatment with iron chelation therapy in patients with lower-risk myelodysplastic syndromes participating in the European MDS registry

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Supplementary Material

Supplementary Method Section

General

In the EUMDS registry, clinical information was collected via a bespoke web-based database on: concomitant diseases, transfusion history, use of iron chelators (chelating agent, start date and end date; no drug doses or schedules were collected), peripheral blood values, conventional iron parameters (serum ferritin, transferrin saturation), concomitant treatments (lenalidomide, erythroid stimulating agents [ESA], and hypomethylating therapy), and bone marrow pathology.

As information is recorded at 6-monthly time-points and the patients may have reached the criteria for using iron chelation therapy between visits, the visit prior to reaching the criteria was selected.

Propensity score matched method

The main purpose of PSM was to balance the distribution of observed covariates at the time of meeting the eligibility criteria in both the chelated and non-chelated groups, so there should be no systematic differences in the distribution and overlap of covariates between the two groups after matching.[20] The causal effect of ICT on outcome was estimated in two stages. In the first stage, the propensity score (PS) or the conditional probability of receiving ICT among eligible subjects were estimated using multivariate logistic regression using the characteristics below, identified a priori to be involved in the decision to treat a patient with ICT; A PS graph was used to check visually if the common support condition was satisfied, i.e. if there was sufficient overlap.[21] To examine the balance in this study, we computed standardized differences that were defined as the difference between chelated and non-chelated means of each factor, divided by the pooled standard deviation. Absolute values of standardized differences <0.1 indicated sufficient balance.[20] A p-value of 0.01 or lower was considered to be statistically significant.

Missing data in PS estimations could result in biased estimates, and it may also shrink the pool of potential matches. The following methods were used to impute missing values: 1) last observation carried forward (LOCF) approach: For many patients bone marrow assessments were not repeated after initial diagnosis, accordingly karyotype and bone marrow blast count, required for the calculation of the IPSS-R at each visit, may be missing. A LOCF approach for only these two components of the IPSS-R was applied; 2) Multiple imputation (MI) approach: For missing values of RBCT intensity, serum ferritin level, MDS comorbidity index, Karnofsky performance status, and IPSS-

R, a MI approach was applied to create 20 multiple complete data sets consisting of all non-chelated patients and all visits since the last visit prior to meeting the eligibility criteria.[22] The imputation model also included age, sex, and cumulative RBCT units.

Transfusion dose density

We used the beginning of the time interval in which the first transfusion started after diagnosis as the starting point of time to calculate the cumulative number of transfusion units received and time interval by the end of each subsequent visit. Transfusion dose density was calculated by dividing the cumulative number of units by the time since the starting time point and standardised to monthly value.

Supplementary tables

Supplementary Table 1 Description of iron chelator use

	Unmatched Sample		Matched	Sample
	N	%	N	%
No iron chelation	490	71.12	591	75.00
Deferasirox only	135	19.59	134	17.01
Deferoxamine only	30	4.35	29	3.68
Deferiprone only	12	1.74	12	1.52
Deferasirox and deferoxamine	13	1.89	13	1.65
Deferasirox and deferiprone	4	0.58	4	0.51
Deferoxamine and deferiprone	2	0.29	2	0.25
All of the three	3	0.44	3	0.38
Total	689	100	461	100

Supplementary table 2 Baseline characteristics for all unmatched transfused non-chelated and chelated patients with missing values and imputed values

Covariates	Unmatched data with missing values						Unmatched data with imputations*					
	Non-chelated *N*= 490		Chelated *N*= 199		*P*-Value	*Standardised*	Non-chelated *N*= 490		Chelated *N*= 199		*P*-Value	*Standardised differences***
Age (years)	76 (10)		70 (9)		0,000	-0,554	76 (10)		70 (9)		0,000	-0,554
Sex					0,405	0,070					0,405	0,070
Female	194	39,6%	72	36,2%			194	39,6%	72	36,2%		
Male	296	60,4%	127	63,8%			296	60,4%	127	63,8%		
RBCT Intensity (per month)	0,5 (0,8)		0,6 (1,0)		0,038	0,169	0,5 (0,8)		0,6 (1,0)		0,046	0,161
Ferritin level (ug/L, median, p25-p75)	547,0 (251.2-878.8)		675,0 (434.9-992)		0,046	0,204	693,5 (382-884)		685,8 (504-921)		0,152	0,124
Comorbidity (MDSCI)					0,001	-0,291					0,001	-0,296
Low risk	308	63,2%	150	75,8%			309	63,1%	151	75,9%		
Intermediate risk	149	30,6%	43	21,7%			151	30,8%	43	21,6%		
High risk	30	6,2%	5	2,5%			30	6,1%	5	2,5%		
Performance status					0,001	0,313					0,001	0,290
Unable to care for self	8	2,0%	1	0,6%			8	1,6%	1	0,5%		
Unable to work	132	32,3%	36	20,2%			151	30,8%	39	19,6%		
Able to work and normal activity	269	65,8%	141	79,2%			331	67,6%	159	79,9%		
Prognostic indicator (IPSS-R)					0,138	-0,137					0,106	-0,139
Very low	48	12,0%	22	12,7%			49	10,0%	22	11,1%		
Low	199	49,9%	95	54,9%			276	56,3%	121	61,1%		
Intermediate	111	27,8%	46	26,6%			124	25,3%	45	22,7%		
High	38	9,5%	9	5,2%			38	7,8%	9	4,5%		
Very high	3	0,8%	1	0,6%			3	0,6%	1	0,5%		
Country					0,001	-0,283					0,001	-0,283
Austria	22	4,5%	10	5,0%			22	4,5%	10	5,0%		
Croatia	3	0,6%	1	0,5%			3	0,6%	1	0,5%		
Czech Republic	39	8,0%	25	12,6%			39	8,0%	25	12,6%		
Denmark	24	4,9%	8	4,0%			24	4,9%	8	4,0%		
France	88	18,0%	40	20,1%			88	18,0%	40	20,1%		
Germany	7	1,4%	8	4,0%			7	1,4%	8	4,0%		
Greece	34	6,9%	23	11,6%			34	6,9%	23	11,6%		
Israel	20	4,1%	5	2,5%			20	4,1%	5	2,5%		
Italy	19	3,9%	5	2,5%			19	3,9%	5	2,5%		
Netherlands	10	2,0%	8	4,0%			10	2,0%	8	4,0%		
Poland	15	3,1%	9	4,5%			15	3,1%	9	4,5%		
Portugal	15	3,1%	1	0,5%			15	3,1%	1	0,5%		
Romania	11	2,2%	11	5,5%			11	2,2%	11	5,5%		
Republic of Serbia	7	1,4%	2	1,0%			7	1,4%	2	1,0%		
Spain	32	6,5%	5	2,5%			32	6,5%	5	2,5%		
Sweden	34	6,9%	20	10,1%			34	6,9%	20	10,1%		
UK	110	22,4%	18	9,0%			110	22,4%	18	9,0%		

Note: Continuous variables are reported as mean (standard deviation), while categorical variables are reported as number(percent)

* Multiple imputations in RBCT intensity, ferritin level, comorbidity, performance status, and IPSS-R at eligibility criteria for unchelated patients

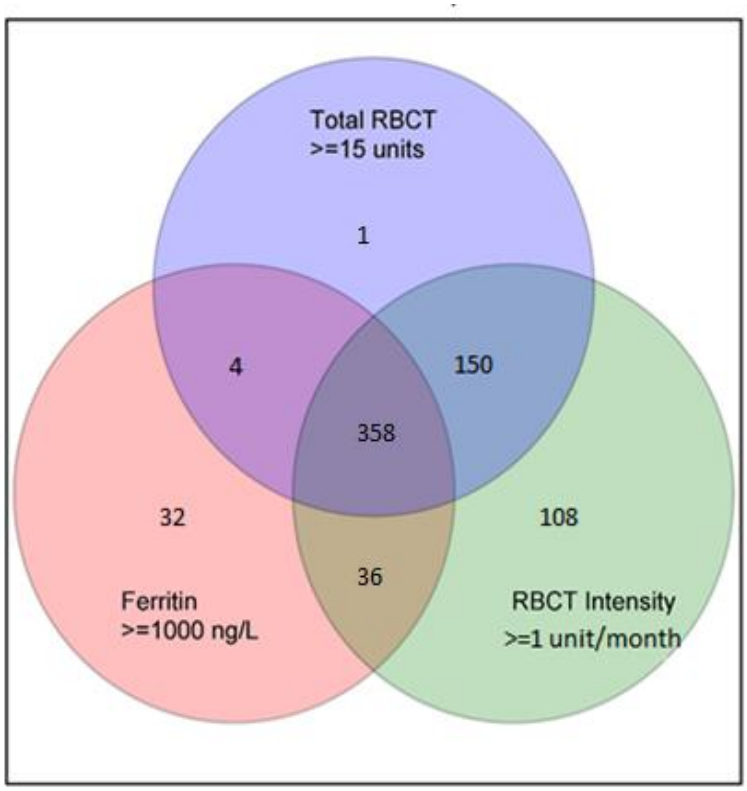
** The standardised difference in percent is the the mean difference as a percentage of the average standard deviation

*** Adjusted by age, sex, comorbidity, performance status, RBCT intensity, number of units transfused, IPSS-R, and RS present

RBCT: red blood cell transfusion; MDSCI: myelodysplastic syndrome specific comorbidity index; IPSS-R: revised international prognostic scoring system; EQ-5D: European Quality of Life - 5 dimensions

Supplementary figures

Supplementary figure 1 Proportion of subjects meeting the eligibility criteria (n=689)



RBCT = Red Blood Cell Transfusion

Supplementary figure 2 Overlap of propensity scores for the chelated and non-chelated groups.