Effects of erythropoiesis-stimulating agents on overall survival of International Prognostic Scoring System Low/Intermediate-1 risk, transfusion-independent myelodysplastic syndrome patients: a cohort study

Clinical guidelines recommend the use of erythropoietin-stimulating agents (ESA) in anemic patients with lower risk myelodysplastic syndrome (MDS)[1-4] and two registration trials for ESA have just been completed.[5,6] We conducted a retrospective study in MDS patients selected by the characteristics predictive of ESA response,[7,8] treated in common practice and enrolled in the Italian network of regional MDS registries (ClinicalTrials.gov Identifier: NCT02808858) within the *Fondazione Italiana Sindromi Mielodisplastiche* (FISM).

The aims of our study were to assess the impact of ESA treatment on overall survival[9] and on the evolution of MDS into acute myeloid leukemia (AML)[10] and to explore the influence of hematologic response on overall survival in the subgroup treated with ESA. We included patients who had *de novo* MDS (between 1999-2013), were aged ≥18 years at diagnosis, had International

Table 1. Characteristics of patients evaluated in the study.

	Non-ESA-treated patients (N=387)		ESA-treated patients (N=758)		All patients (N=1145)		*P*
	N.	%	N.	%	N.	%	
Gender							0.404
Female	159	41.09	331	43.67	490	42.79	
Male	228	58.91	427	56.33	655	57.21	
Age at diagnosis (years)							0.001
≤60	44	11.37	45	5.94	89	7.77	
60-70	87	22.48	164	21.64	251	21.92	
70-80	174	44.96	329	43.40	503	43.93	
>80	82	21.19	220	29.02	302	26.38	
Hemoglobin (g/dL)							<0.001
≤ 8	72	18.6	96	12.66	168	14.67	
8-10	134	34.63	446	58.84	580	50.66	
10-12	181	46.77	216	28.50	397	34.67	
IPSS risk group							<0.001
Low	167	43.15	425	56.07	592	51.7	
Intermediate-1	220	56.85	333	43.93	553	48.3	
Revised IPSS risk group							<0.001
Very low	85	21.96	154	20.32	239	20.86	
Low	149	38.5	400	52.77	549	47.95	
Intermediate	72	18.6	96	12.66	168	14.66	
High	24	6.2	26	3.43	50	4.36	
Very high	2	0.52	0	0	2	0.2	
Not evaluable	55	14.22	82	10.82	137	11.97	
Cytogenetics							0.388
Very good	15	3.88	31	4.09	46	4.02	
Good	292	75.45	592	78.1	884	77.21	
Intermediate	34	8.79	73	9.63	107	9.34	
Poor	5	1.29	5	0.66	10	0.87	
Very poor	3	0.78	2	0.26	5	0.44	
Not recorded	38	9.82	55	7.26	93	8.12	
Diagnosis (WHO 2008)							<0.001
RA	108	27.91	264	34.83	372	32.49	
RARS	23	5.94	91	12.01	114	9.96	
RAEB1	92	23.77	80	10.55	172	15.02	
Del(5q)	14	3.62	39	5.15	53	4.63	
MDS-U	23	5.94	12	1.58	35	3.06	
RCMD	127	32.82	272	35.88	399	34.85	
Erythropoietin alpha							
No			87	11.48			
Yes			502	66.23			
Not recorded			169	22.3			

ESA: erytrhropietin-stimulating agent; IPSS: International Prognostic Scoring System; WHO: World Health Organization; RA: refractory anemia; RARS: RA with ringed sideroblasts; RAEBI: RA with excess blasts I; MDS-U: myelodysplastic syndrome unclassified; RCMD: refractory cytopenia with multilineage dysplasia.

Prognostic Scoring System (IPSS)-Low or Intermediate-1 (Int-1) risk disease,[11] had a baseline hemoglobin (Hb) ≤12.0 g/dL and who had not been previously treated with disease-modifying agents (lenalidomide/azacitidine). We excluded patients with a baseline erythropoietin level >500 U/L or who were transfusion-dependent (>2 red blood cell units/4 weeks) according to Nordic group scoring.[7]

Erythropoietin (alpha in the majority of cases, or beta) was administered at doses ranging between 30000 - 80000 U/week, according to the physicians' choice, for at least 12 weeks. Erythroid improvement (HI-E) was eva-luated applying International Working Group (IWG) 2006 criteria.[12]

The distribution of patients' characteristics was summarized using percentiles, for continuous variables, and percentages and frequencies for categorical variables. Overall survival was defined as the time from diagnosis of MDS to death or to the last follow-up date. We estimated the effect of ESA treatment on overall survival using a Cox proportional hazard model that included a pre-defined set of known risk factors for mortality (age, sex, Hb level, IPSS category, diagnosis and cytogenetics), and ESA treatment as a time-dependent covariate, in

Table 2. Crude and adjusted effects of clinical variables and treatment with an erythropoiesis-stimulating agent on overall survival (Cox model) and on progression to acute myeloid leukemia (Fine and Gray model).

	Overall survival (n=1145, 402 deaths) Cox model						AML evolution(n=997, 74 AML) Fine and Gray model					
	Crude effect			Adjusted effect			Crude effect			Adjusted effect		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Gender												
Female	1			1			1			1		–
Male	1.55	[1.26,1.91]	<0.001	1.59	[1.29,1.97]	<0.001	0.97	[0.61;1.53]	0.887	0.87	[0.52,1.43]	0.577
Age at diagnosis (years)	1.06	[1.05,1.08]	<0.001	1.06	[1.05,1.08]	<0.001	1.01	[0.99,1.02]	0.507	1.00	[0.98,1.02]	0.927
≤60	1						1					
60-70	1.70	[1.01,2.86]	0.046				1.22	[0.50,2.95]	0.661			
70-80	3.16	[1.93,5.15]	<0.001				1.38	[0.61,3.12]	0.438			
>80	5.72	[3.45,9.48]	<0.001				0.96	[0.38,2.41]	0.931			
Hemoglobin (g/dL)	0.76	[0.71,0.81]	<0.001				0.82	[0.70,0.95]	0.011			
Hemoglobin (g/dL)												
≤8	1			1			1			1		–
8-10	0.62	[0.48,0.79]	<0.001	0.66	[0.51,0.85]	0.002	0.54	[0.30,0.96]	0.036	0.54	[0.30,0.98]	0.043
>10	0.32	[0.24,0.43]	<0.001	0.34	[0.25,0.46]	0.000	0.38	[0.20,0.73]	0.004	0.48	[0.25,0.93]	0.029
IPSS risk group												
Low	1						1					
Intermediate-1	1.99	[1.63,2.42]	<0.001				3.01	[1.82,4.99]	<0.001			
Diagnosis (WHO 2008)												
RA	1.00			1		–	1			1		–
RARS	0.88	[0.60,1.30]	0.520	0.77	[0.52,1.14]	0.197	0.91	[0.30,2.80]	0.876	0.84	[0.27,2.58]	0.755
RAEB1 (<10% blasti)	3.66	[2.78,4.81]	<0.001	3.18	[2.40,4.21]	0.000	6.45	[3.30,12.62]	<0.001	6.74	[3.38,13.44]	<0.001
RCMD	1.42	[1.09,1.84]	0.008	1.42	[1.09,1.85]	0.009	1.85	[0.92,3.71]	0.083	1.98	[0.97,4.06]	0.061
Others	1.38	[0.94,2.05]	0.104	1.57	[1.05,2.34]	0.026	2.25	[0.89,5.69]	0.085	2.39	[0.94,6.09]	0.068
Cytogenetics												
Very good/good	1			1	[1.00,1.00]	–	1			1	[1.00,1.00]	–
Intermediate/poor/very poor	1.00	[0.72,1.39]	0.983	1.36	[0.98,1.89]	0.068	1.68	[0.91,3.10]	0.097	1.98	[1.02,3.83]	0.043
Not recorded	1.08	[0.75,1.54]	0.681	1.12	[0.78,1.61]	0.542	0.79	[0.29,2.18]	0.650	0.89	[0.32,2.49]	0.818
Serum erythropoietin ≤ 500 U/L												
Yes	1						1					
Not recorded	1.04	[0.85,1.26]	0.716				0.77	[0.49,1.22]	0.273			
ESA treatment (changes with time)												
No	1			1								
Yes	0.89	[0.73,1.09]	0.251	0.85	[0.69,1.04]	0.119						
ESA treatment within 6 months of diagnosis												
No							1			1		.
Yes							1.29	[0.82,2.02]	0.276	1.47	[0.92,2.33]	0.106

IPSS: International Prognostic Scoring System; WHO: World Health Organization; RA: refractory anemia; RARS: RA with ringed sideroblasts; RAEBI: RA with excess blasts I; RCMD: refractory cytopenia with multilineage dysplasia; ESA: erythropoiesis-stimulating agent.

order to reduce the immortal time bias (ESA-treated patients were analyzed in the group not treated with ESA until they received the first dose of an ESA, and in the ESA group thereafter).

The effect of ESA on overall survival was assessed in subgroups defined by sex, age (≤70, >70 years), Hb level at diagnosis (≤ 8, >8-10, >10-12 g/dL), World Health Organization 2008 diagnosis [refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), del(5q), refractory cytopenia with multilineage dysplasia (RCMD), MDS-unclassified (MDS-U), refractory anemia with excess blasts (RAEB-1)] and cytogenetic categories.[13] Interaction tests between ESA and each stratifying variable were used to detect effect modifications.

In the ESA-treated patients, we estimated the effect of HI-E on overall survival using a Cox proportional hazard model including the same potential confounders as in the previous analysis and HI-E as a time-dependent covariate, excluding the first 6 months of follow-up (landmark analysis). The proportional hazard assumption was tested using Schoenfeld residuals.

The cumulative incidence of evolution to AML was estimated considering death from any cause as a competing event. In order to estimate the effect of ESA treatment (within 6 months of the diagnosis of MDS) on the risk of developing AML, we used the Fine and Gray model adjusting for the same set of potential confounders as that used for overall survival.

Among 3438 patients in the MDS registries, 1145 satisfied the eligibility criteria, had complete records and were analyzed (*Online Supplementary Figure S1*). These patients' characteristics are shown in Table 1. Overall, 758 patients (66%) received an ESA, and 82% of them started treatment within 6 months of diagnosis. IPSS risk was low in 592 (52%) and intermediate-1 in 553 (48%). The revised IPSS (IPSS-R) was assessed for 1008 patients. Nearly 30% of ESA-treated patients were >80 years old, 28.5% had moderate anemia, 56% had low-risk IPSS, and 47% had RA/RARS. As expected, patients not treated with ESA were younger, had significantly higher levels of Hb, and a lower proportion (34%) had RA/RARS.

The overall survival rates at 12, 24, 36 and 60 months after diagnosis were 91.8% (95% CI: 89.9-93.3), 80.8% (95% CI: 78.1-83.1), 71.2% (95% CI: 68.1-74.1) and 57.5% (95% CI: 53.6-61.1), respectively (Figure 1A).

No statistically significant difference in overall survival at 24 months was detected according to ESA treatment, although patients receiving ESA had lower hazard ratios (HR) in both univariate (crude HR=0.89; 95% CI: 0.73-1.09; *P*=0.251) and multivariate analyses (adjusted HR=0.85; 95% CI: 0.69-1.04; *P*=0.119).

Irrespective of treatment, male sex, increasing age, and any diagnosis of MDS other than RA or RARS were associated with worse survival. Patients who had IPSS intermediate-1 risk had a significantly worse survival than IPSS low-risk patients (*P*<0.001). Generally, patients with severe anemia at diagnosis (<8 g/dL) had significantly shorter survival than those with Hb >8 g/dL, with hazard ratios of 0.66 (95% CI: 0.51-0.85) and 0.34 (95% CI: 0.25-0.46) for the 8-10 g/dL and 10.1-12 g/dL Hb categories, respectively. Cytogenetic subtypes were not associated with differences in overall survival (Table 2).

A subgroup analysis was performed according to the risk factors included in the multivariable Cox model: a favorable effect of ESA (compared to non-treatment) was suggested for patients with Hb 8-10 g/dL, and with a diagnosis of RA, RARS or del(5q) (*Online Supplementary Figure S1*).

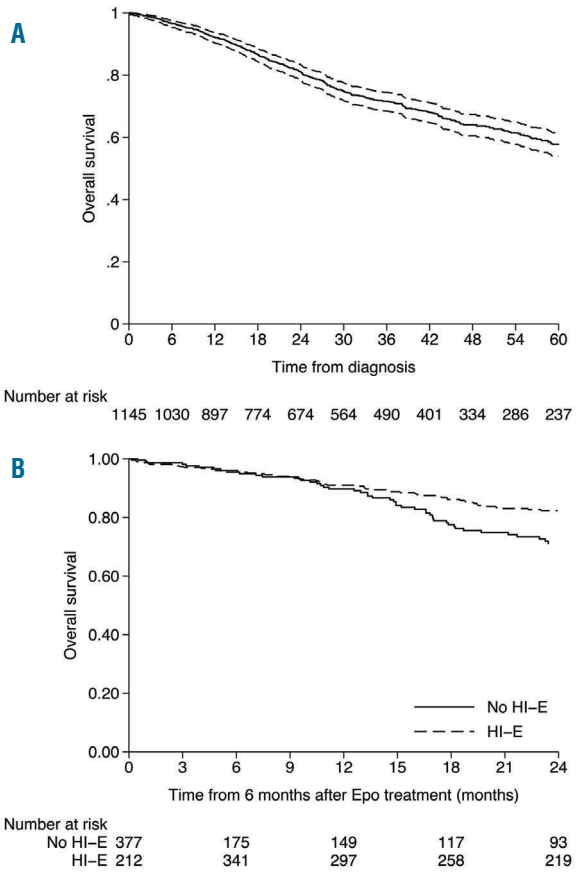

Figure 1. Overall survival of patients with IPSS lower-risk myelodysplastic syndrome. (A) Overall survival of the entire population of lower risk MDS patients analyzed in the study (n=1145), independently of treatment. Overall survival rates at 12, 24, 36 and 60 months after diagnosis were 91.8% (95%CI:89.9-93.3), 80.8 % (95%CI:78.1-83.1), 71.2% (95%CI:68.1-74.1) and 57.5% (95%CI:53.6-61.1), respectively. The 95% confidence interval is represented by the dashed line in the figure. (B) Overall survival of ESA-treated patients (n=589) evaluated after 6 months of therapy, in the absence of hematologic improvement (HI-E; IWG 2006 criteria) (continuous line) or according to achievement of HI-E (dotted line). Epo: erythropoietin.

Among the 758 patients treated with ESA, 109 did not have a registered IWG response during follow up, but maintained treatment. Of the MDS patients classified as IPSS low risk, 72% had responses, whereas the response rate was 76.8% in those with IPSS intermediate-1 risk, 76.8% also in patients with very low risk according to the IPSS-R and 65.6% in those with IPSS-R low risk, confirming our recent observations.[14] The cumulative incidence of HI-E, defined according to IWG 2006 criteria,[12] at 3, 6, 12 and 24 months was 35.45% (95% CI: 15.43-21.39), 38.45% (95% CI: 34.67-42.21), 47.09% (95% CI: 43.14-50.92) and 60.66% (95% CI: 56.62-64.44), respectively. Overall, we did not observe a strong difference in overall survival according to HI-E in ESA-treated patients (HR=0.96; 95% CI: 0.71-1.28; adjusted HR=1.01; 95% CI: 0.73-1.38) (Figure 1B).

The risk of evolution into AML could be analyzed for 1109/1145 patients. Eighty patients developed AML during the follow up. The estimated 5-year cumulative risk of developing AML was 10.4% (95% CI: 8.3-12.8). The risk of AML was estimated to be higher in the RAEB-1 subgroup (sub-distribution HR=6.74; 95% CI: 3.38-

13.44) and for higher risk cytogenetic categories. Having Hb values >8 g/dL showed a protective effect. ESA treatment within 6 months after the diagnosis of MDS was not associated with a risk of AML (sub-distribution HR=1.47; 95% CI: 0.92-2.33).

In this registry-based study we analyzed a large sample of exclusively IPSS lower risk anemic MDS patients with complete clinical records: the majority of MDS lower risk patients received ESA (66%), and, quite correctly according to published evidence,[8] 82% of them within 6 months of diagnosis.[15]

Response rates to ESA in this study are consistent with those in previous publications. We also confirm that response rates are higher in patients in IPSS-R lower risk categories.[14] In this study there was a suggestion of a stronger protective effect of ESA for World Health Organization diagnostic categories with lower percentages of blasts and sole erythroid dysplasia. The overall survival advantage in ESA-treated patients was observed for cases with Hb 8-10 g/dL prior to treatment. However, probably because of limited statistical power, none of these differences by subgroups reached conventional statistical significance. We could not show a global overall survival advantage in MDS patients who responded to ESA, unlike some published studies.[8,10,15] Treatment with ESA per se did not have a protective effect against the evolution of MDS into AML.

Our analysis differs from previous ones in several aspects. Since this is a retrospective analysis, there are limitations due to possible additional unidentified parameters affecting survival. We adopted several measures to reduce the risk of biased evaluation of the effects of ESA. We excluded all patients who had received, prior to the ESA, any other drug, such as lenalidomide or azacitidine, which could potentially affect erythroid function, as well as patients who were transfusion dependent according to IWG criteria. To adjust the comparisons for the unbalanced distribution of some confounders, well-established prognostic factors for MDS were included in the multivariable models. Since ESA treatment was started at different times from diagnosis, it was modeled as a time-varying variable to prevent survival time bias, which was not taken into account in previously published studies. Lastly, when estimating the association of ESA therapy with the risk of evolution to AML, we used a multivariable Fine and Gray model to account for mortality as a competing risk.

Guidelines (slightly differently from the recent approval) recommend ESA for IPSS lower risk patients with Hb <10 g/dL and serum erythropoietin <500 U/L (<200 U/L in the European approval) with no transfusion requirement.[1-4] The data from the Surveillance, Epidemiology, and End Results showed a frequent lack of adherence.[16] We observed that among a group of 397 patients with Hb >10 g/dL, 216 (54%) were treated with ESA, in disagreement with guidelines, and quite notably did not show any advantage with regards to overall survival.

In conclusion, our study confirms the high response rates of IPSS and IPSS-R lower risk MDS patients to ESA treatment and suggests an improvement in survival in treated patients with Hb 8-10 g/dL pre-treatment. We also found a trend for a survival advantage in MDS patients with isolated erythroid dysplasia (RA/RARS/del5q). Our observations obtained in a large cohort of MDS patients should support appropriate, wise use of ESA in clinical practice.

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