RESEARCH ARTICLE

DOI: 10.4274/tjh.galenos.2023.2022.0437
Turk J Hematol 2023;40:92-100

Long-Term Efficacy of Erythropoiesis-Stimulating Agents in Patients with Low-Risk or Intermediate-1-Risk Myelodysplastic Syndrome: Multicenter Real-Life Data

Eritropoezi Stimüle Edici Ajanların Düşük Riskli veya Orta-1 Riskli Myelodisplastik Sendromlu Hastalarda Uzun Dönem Tedavi Etkinliğinin Değerlendirilmesi: Çok Merkezli Gerçek Yaşam Verisi

Müzeyyen Aslaner Ak[1], Ayfer Gedük[2], İbrahim Halil Acar[3], Merve Gökçen Polat[2], Cenk Sunu[4], Ali Zahit Bolaman[5], Tuğba Hacıbekiroğlu[4], Birol Güvenç[3], Şehmus Ertop[1]

[1]*Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Hematology, Zonguldak, Türkiye*
[2]*Kocaeli University Faculty of Medicine, Department of Hematology, Kocaeli, Türkiye*
[3]*Çukurova University Faculty of Medicine, Department of Hematology, Adana, Türkiye*
[4]*Sakarya Training and Research Hospital, Clinic of Hematology, Sakarya, Türkiye*
[5]*Adnan Menderes University Faculty of Medicine, Department of Hematology, Aydın, Türkiye*

Abstract

Objective: This study was undertaken to evaluate the long-term clinical efficacy of epoetin alfa and darbepoetin alfa in patients with myelodysplastic syndrome (MDS) in a real-life setting.

Materials and Methods: A total of 204 patients with low-risk or intermediate-1-risk MDS who received epoetin alfa or darbepoetin alfa were included. Hemoglobin levels and transfusion needs were recorded before treatment and at 12 months, 24 months, 36 months, and 48 months of treatment.

Results: At the 36-month (p=0.025) and 48-month (p=0.022) visits, epoetin alfa yielded significantly higher hemoglobin levels compared to darbepoetin alfa. Transfusion needs were also significantly lower with epoetin alfa compared to darbepoetin alfa at 24 months (p=0.012) and in the low-risk group compared to the intermediate-risk group at 24 months (p=0.018), 36 months (p=0.025), and 48 months (p<0.001). Treatment response rates at the 24-month, 36-month, and 48-month visits in the epoetin alfa (43.0%, 33.6%, and 27.1%), darbepoetin alfa (29.9%, 22.7%, and 16.5%), low-risk (39.3%, 30.0%, and 26.0%), and intermediate-risk (29.6%, 24.1%, and 11.1%) groups were lower than those obtained at 12 months, and the values differed significantly for the 36-month and 48-month visits with values ranging from p<0.05 to p<0.001.

Conclusion: This real-life long-term ESA extension study investigated the clinical efficacy of epoetin alfa and darbepoetin alfa for up to 48 months, revealing that treatment efficacy reached a plateau starting from the 24th month of therapy with a continuing decrease

Öz

Amaç: Myelodisplastik sendromlu (MDS) hastalarda epoetin alfa ve darbepoetin alfa tedavisinin gerçek yaşam ortamında uzun-dönem klinik etkinliğini değerlendirmek.

Gereç ve Yöntemler: Bu çalışmaya düşük veya orta-1 risk grubu MDS tanısı ile epoetin alfa veya darbepoetin alfa tedavisi almış 204 hasta dahil edildi. Hemoglobin düzeyleri ve transfüzyon gereksinimi, tedaviden önce ve tedavinin 12., 24., 36. ve 48. aylarında değerlendirildi.

Bulgular: Epoetin alfa, darbepoetin alfa ile kıyaslandığında, 36. ay (p=0,025) ve 48. aylarda (p=0,022) anlamlı şekilde daha yüksek hemoglobin düzeylerini sağladı. Transfüzyon gereksinimi 24. ayda (p=0,012) epoetin alfa grubunda darbepoetin alfa grubuna göre, 24. ay (p=0,018), 36. ay (p=0,025) ve 48. aylarda (p<0,001) ise düşük risk grubunda orta risk grubuna göre anlamlı şekilde daha düşük olarak bulundu. Tedavi yanıt oranları 24. ay, 36. ay ve 48. aylarda epoetin alfa (%43,0, %33,6 ve %27,1), darbepoetin alfa (%29,9, %22,7 ve %16,5), düşük risk (%39,3, %30,0 ve %26,0) ve orta risk (%29,6, %24,1 ve %11,1) gruplarında 12. ay yanıt oranlarına göre daha düşük olup, 36. ve 48. aylarda bu değişim istatistiksel olarak anlamlı idi (p<0,05 ile <0,001 arası).

Sonuç: Epoetin alfa ve darbepoetin alfanın 48 aylık klinik etkililiğinin değerlendirildiği bu gerçek-yaşam uzun-dönem ESA çalışmasında, tedavi etkililiğinin tedavinin 24. ayından başlayarak plato evresine eriştiği ve devamında tedavi yanıt oranlarında, tedavi tipi, risk durumu veya cinsiyetten bağımsız olarak süregiden bir düşüşün gerçekleştiği saptandı. Bununla birlikte, epoetin tedavisi alan grupta darbepoetin ile tedavi edilen gruba göre ve düşük risk grubu hastalarda orta

Address for Correspondence/Yazışma Adresi: Müzeyyen Aslaner Ak, M.D., Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Hematology, Zonguldak, Türkiye
Phone : + 90 505 485 48 53
E-mail : drmaslaner@hotmail.com ORCID: orcid.org/0000-0001-6621-3138

Received/Geliş tarihi: September 30, 2022
Accepted/Kabul tarihi: February 15, 2023

in treatment response rates regardless of treatment type, risk status, or gender. Nonetheless, significantly higher hemoglobin levels and marked improvement in transfusion needs were evident in epoetin-treated patients compared to darbepoetin-treated patients and in the low-risk group compared to the intermediate-risk group.

Keywords: Myelodysplastic syndrome, Low-risk, Intermediate-1-risk, Epoetin alfa, Darbepoetin alfa, Long-term, Treatment response, Duration of response, Transfusion dependence

risk grubu hastalara göre, hemoglobin düzeyleri anlamlı şekilde daha yüksek olup, transfüzyon gereksiniminde de belirgin azalma olduğu tespit edildi.

Anahtar Sözcükler: Myelodisplastik sendrom, Düşük risk, Orta-1 risk, Epoetin alfa, Darbepoetin alfa, Uzun-dönem, Tedavi yanıtı, Yanıt süresi, Transfüzyon bağımlılığı

Introduction

Epoetin alfa (short-acting) and darbepoetin alfa (long-acting) are commonly used erythropoiesis-stimulating agents (ESAs) in clinical practice for the treatment of anemia in patients with low-risk or intermediate-1-risk myelodysplastic syndrome (MDS) to reduce the transfusion requirements and transfusion-related risks [1,2,3,4,5]. However, the ESA response rates in routine practice may differ from those reported in clinical trials with the use of higher doses of ESAs [6,7]. The value of continuing ESAs in the absence of an early response also remains unclarified due to investigations of response rates rather than durations of response in most previous ESA studies [3,8,9,10,11].

We previously reported the comparative efficacy of 12-month epoetin alfa and darbepoetin alfa treatments in improving hemoglobin levels and reducing transfusion needs in patients with low-risk or intermediate-1-risk MDS in a real-life setting [12]. The present extension study aims to evaluate the long-term clinical efficacy of epoetin alfa and darbepoetin alfa in terms of the rate and durability of treatment response and transfusion dependence for up to 48 months in patients with low-risk or intermediate-1-risk MDS in a retrospective real-life setting.

Materials and Methods

Study Population

A total of 204 patients newly diagnosed with low-risk or intermediate-1-risk MDS who received ESA treatment with epoetin alfa (Eporon®, Dem Pharmaceuticals; maintenance: 75-300 U/kg per week; maximum dose: 900 U/kg per week) or darbepoetin alfa (Aranesp®, Amgen Pharmaceuticals; maintenance: 0.13-0.35 µg/kg per week; maximum dose: 150 µg per week) after the diagnosis were included in this retrospective multicenter, non-interventional hospital registry study. Pretreatment erythropoietin (EPO) levels of <500 IU/mL and the presence of hemoglobin levels of <10 g/dL with or without a need for ≥2 units of erythrocyte suspension transfusion per month were the inclusion criteria of the study. Patients with high-risk MDS, acute myeloid leukemia, EPO levels of >500 IU/mL, hemoglobin levels of >12 g/dL, anemia related to iron deficiency or chronic disease, uncontrolled hypertension or chronic kidney disease, or any MDS treatments other than ESAs were excluded.

Written informed consent was obtained from each patient following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the relevant institutional ethics committee (date of approval: 01/12/2021; protocol no: 2021/23).

Data Collection

Data on baseline characteristics including patient demographics, EPO and hemoglobin levels, transfusion needs, and type of ESA treatment were recorded. Data on hemoglobin levels and transfusion needs were recorded in the pretreatment period as well as at four consecutive visits (12-month, 24-month, 36-month, and 48-month visits) after the onset of treatment. Treatment response was evaluated in subgroups according to ESA treatments (epoetin alfa vs. darbepoetin alfa), risk groups (low vs. intermediate risk), and genders (female vs. male).

MDS Diagnosis, Risk Groups, and Treatment Response

MDS risk stratification and assessments of response to treatment were performed as previously described [13,14].

ESA Treatments

Treatment doses for epoetin alfa (Eporon®, Dem Pharmaceuticals; initial dose of 50-150 U/kg per week, maintenance: 75-300 U/kg per week; maximum dose: 900 IU/kg per week) and darbepoetin alfa (Aranesp®, Amgen Pharmaceuticals; initial dose of 0.25-0.75 µg/kg per week; maintenance: 0.13-0.35 µg/kg per week; maximum dose: 150 µg/kg per week) were determined in accordance with the Turkish Ministry of Health's Health Implementation Directive.

Treatment was continued until the loss of response in any cases. For patients with failure to achieve treatment response or those with partial erythroid response (50% reduction in transfusion need) after at least 8 weeks of regular treatment, dose increments were applied. For patients who failed to achieve sufficient treatment responses despite the maximum dose of ESA, treatment was discontinued at weeks 16-24. Cross-over was not allowed in accordance with local regulations. Patients with low serum ferritin levels under treatment received iron supplementation therapy.

Statistical Analysis

Statistical analysis was performed using MedCalc Statistical Software version 12.7.7 (MedCalc Software, Ostend, Belgium; http://www.medcalc.org; 2013). Cochran's Q test and the post hoc McNemar test with Bonferroni correction were used for comparisons of categorical data, while numerical data were analyzed using the Student t-test and Mann-Whitney U test for variables with normal distribution and non-normal distribution, respectively. Change over time was analyzed via repeated-measures ANOVA with Bonferroni corrections. Data were expressed as mean ± standard deviation, minimum-maximum, and percentage (%) as appropriate. Values of $p<0.05$ were considered statistically significant.

Results

Baseline Characteristics

No significant difference was noted between treatment groups in terms of baseline characteristics (Table 1).

Hemoglobin Levels

In both the epoetin alfa and darbepoetin alfa groups, hemoglobin levels were significantly higher at the 12th month compared to pretreatment levels ($p<0.001$ for each). Hemoglobin levels at later visits (24, 36, and 48 months) showed no significant changes from the baseline hemoglobin levels (Table 2).

Epoetin alfa yielded significantly higher hemoglobin levels compared to darbepoetin alfa at the 36-month ($p=0.025$) and 48-month ($p=0.022$) visits (Table 2, Figure 1).

Hemoglobin levels were significantly higher in the low-risk group compared to the intermediate-1-risk group in the pretreatment period and at each follow-up visit, with significance values ranging from $p=0.014$ to $p<0.001$ (Table 3, Figure 1).

In each risk group, hemoglobin levels were significantly increased from baseline at the 12-month visit regardless of gender (Table 3).

Transfusion Needs

A significant decrease in transfusion needs from the baseline was evident at each follow-up visit in the epoetin alfa group ($p<0.001$ for each visit) and in the low-risk group (from $p<0.01$ to $p<0.001$). In the darbepoetin alfa and intermediate-1 risk groups, there was no significant change from baseline in transfusion needs during the follow-up visits (Table 4).

Transfusion needs were significantly lower in the epoetin alfa group compared to the darbepoetin alfa group at 24 months ($p=0.012$) and in the low-risk group compared to the intermediate-1-risk group at 24 months ($p=0.018$), 36 months ($p=0.025$), and 48 months ($p<0.001$) (Table 4).

Percentage of Patients with Treatment Response (≥1.5 g/dL Increase in Hemoglobin)

The 24-month, 36-month, and 48-month treatment response rates in the epoetin alfa (43.0%, 33.6%, and 27.1%), darbepoetin alfa (29.9%, 22.7%, and 16.5%), low-risk (39.3%, 30.0%, and 26.0%), and intermediate-1-risk (29.6%, 24.1%, and 11.1%) groups were lower than the 12-month response rates, but the decrease was only significant at the 36-month and 48-month visits (from $p<0.05$ to $p<0.001$). The lowest response rates were achieved at 48 months in the darbepoetin alfa and intermediate-1-risk groups ($p<0.05$ for each) (Table 5).

Table 1. Baseline characteristics.

		Total (n=204)	Epoetin alfa (n=116)	Darbepoetin alfa (n=88)	p
Age (years)	Mean ± SD	72.0±10.0	71.6±10.6	72.5±10.3	0.415[1]
	Median (min-max)	72.0 (35.0-95.0)	72 (39-93)	73.5 (35-95)	
Gender, n (%)					
Female		119 (58.3)	71 (61.2)	48 (54.5)	0.390[2]
Male		85 (41.7)	45 (38.8)	40 (45.5)	
Risk group, n (%)					
Low		170 (83.3)	99 (85.3)	71 (80.7)	0.449[2]
Intermediate-1		34 (16.7)	17 (14.7)	17 (19.3)	
Transfusion need, n (%)					
Yes		80 (39.2)	49 (42.2)	31 (35.2)	0.316[2]
No		124 (60.8)	67 (57.8)	57 (64.8)	
Hemoglobin level (g/dL)	Mean ± SD	8.74±1.04	8.7±1	8.8±1.1	0.275[1]
	Median (min-max)	8.8 (5.1-11.0)	8.7 (5.9-10.9)	9.05 (5.1-11)	

[1]Mann-Whitney U test; [2]chi-square test; min: minimum; max: maximum.

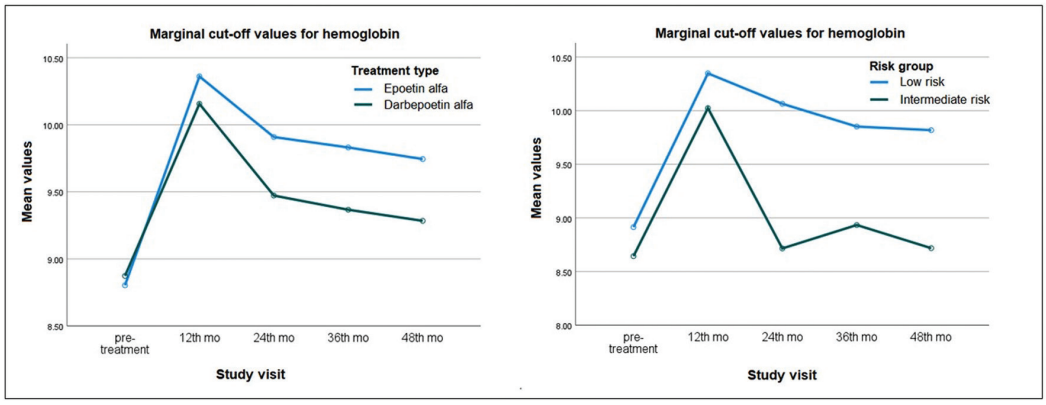

Figure 1. Marginal cut-off values for hemoglobin according to treatment type and risk groups.
mo: month.

Table 2. Hemoglobin levels according to treatment and gender.

		Hemoglobin levels (g/dL)					p[a]		
Treatment groups		**Pretreatment**	**12th month**	**24th month**	**36th month**	**48th month**	**p[1]**	**p[2]**	**p[3]**
Epoetin alfa	Mean ± SD	8.8±0.9	10.4±1.4*	9.9±1.4	9.8±1.3	9.7±1.1	<0.001	0.052	0.131
	Median (min-max)	8.8 (6.5-10.9)	10.4 (5.7-13.1)	10.1 (7.1-12.2)	9.9 (7.0-12.8)	9.8 (7.2-13.7)			
Darbepoetin alfa	Mean ± SD	8.9±1.0	10.2±1.5	9.5±1.6	9.4±1.2	9.3±1.1			
	Median (min-max)	8.9 (5.5-11.0)	10.6 (6.1-12.9)*	9.4 (6.4-13)	9.3 (5.8-12.9)	9.4 (6.4-12)			
	p	0.254[b]	0.811[b]	0.086[b]	0.025[c]	0.022[c]			
Gender in treatment groups		**Pretreatment**	**12th month**	**24th month**	**36th month**	**48th month**	**p[1]**	**p[2]**	**p[3]**
Epoetin alfa									
Female	Mean ± SD	8.8±1.0	10.1±1.5*	10.1±1.5	10.0±1.4	9.9±1.2	<0.001	0.491	**0.008**
	Median (min-max)	8.8 (6.5-10.9)	10.4 (5.7-12.4)	10.3 (7.2-12.2)	10.3 (7-12.8)	10 (7.5-13.7)			
Male	Mean ± SD	8.8±0.8	10.7±1.2*	9.7±1.2	9.6±1.1	9.5±0.9			
	Median (min-max)	8.7 (7.7-10.3)	10.9 (7.7-13.1)	9.5 (7.1-12)	9.5 (7.3-12.3)	9.8 (7.2-11.1)			
	p[b]	0.786	0.191	0.153	0.081	0.138			
Darbepoetin alfa									
Female	Mean ± SD	8.8±1.3	10.3±1.4*	9.8±1.6	9.5±1.2	9.6±0.9	<0.001	0.105	0.235
	Median (min-max)	8.9 (5.5-11)	10.8 (7-12.8)	9.6 (7-13)	9.3(8-12.9)	9.5 (7.9-12)			
Male	Mean ± SD	8.9±0.8	10±1.6*	9.2±1.6	9.2±1.3	9±1.1			
	Median (min-max)	8.9 (7.4-10.4)	10.6 (6.1-12.9)	9 (6.4-12)	9.3 (5.8-11.2)	9.2 (6.4-10)			
	p[b]	0.925	0.991	0.219	0.967	0.056			

[a]Mixed ANOVA: [1]between visits; [2]between epoetin alfa and darbepoetin alfa (main group effect); [3]between epoetin alfa and darbepoetin alfa between visits (measurement x group effect).
[b]Mann-Whitney U test, [c]Student t-test.
*p<0.001 compared to pretreatment levels (post hoc Bonferroni correction with p<0.005).
SD: Standard deviation; min: minimum; max: maximum.

Discussion

This real-life long-term ESA extension study revealed that treatment efficacy reached a plateau starting from the 24th month of therapy with a continuing decrease in treatment response rates regardless of treatment type, risk status, or gender. Nonetheless, hemoglobin levels were significantly higher alongside more prominent improvement in transfusion dependency and a slower decrease in treatment response rates from baseline in epoetin-treated patients compared to

Table 3. Hemoglobin levels according to risk groups and genders.

		Hemoglobin levels (g/dL)					p[a]		
Risk groups		**Pretreatment**	**12th month**	**24th month**	**36th month**	**48th month**	**p[1]**	**p[2]**	**p[3]**
Low risk	Mean ± SD	8.9±1.0	10.3±1.4**	10.1±1.4	9.9±1.2	9.8±1.0	<0.001	<0.001	<0.001
	Median (min-max)	9.0 (5.5-11.0)	10.5 (5.7-13.1)	10.2 (6.9-12.6)	9.8 (6.8-12.9)	9.8 (7.5-13.7)			
Intermediate-1 risk	Mean ± SD	8.6±0.7	10±1.5**	8.7±1.5	8.9±1.2	8.7±1			
	Median (min-max)	8.5 (7-9.9)	10.7 (6.1-11.9)	8.6 (6.4-13)	8.9 (5.8-11.4)	8.8 (6.4-10.7)			
	p[b]	0.014	0.043	<0.001	<0.001	<0.001			
Gender in risk groups		**Pretreatment**	**12th month**	**24th month**	**36th month**	**48th month**	**p[1]**	**p[2]**	**p[3]**
Low risk									
Female	Mean ± SD	8.9±1.1	10.2±1.5**	10.2±1.4	10±1.3	10±1.1	<0.001	0.505	<0.001
	Median (min-max)	8.9 (5.5-11.0)	10.4 (5.7-12.8)	10.3 (7.1-12.6)	10 (7-12.9)	10 (8.1-13.7)			
Male	Mean ± SD	8.9±0.9	10.6±1.3** [4]	9.9±1.3	9.7±1.1	9.6±0.9			
	Median (min-max)	9 (7.4-10.4)	10.9 (6.9-13.1)	10 (6.9-12)	9.7 (6.8-12.3)	9.8 (7.5-11.1)			
	p[b]	0.879	0.059	0.376	0.221	0.115			
Intermediate-1 risk									
Female	Mean ± SD	8.5±0.8	10.3±1.4*	9.1±1.7	9.1±1.1	9.0±0.8	<0.001	0.179	0.304
	Median (min-max)	8.5 (7-9.8)	10.9 (7-11.9)	8.8 (7-13)	9 (7-11.4)	9.3 (7.5-10.7)			
Male	Mean ± SD	8.8±0.6	9.8±1.6*	8.4±1.2	8.8±1.3	8.5±1.1			
	Median (min-max)	8.5 (7.9-9.9)	10 (6.1-11.8)	8.4 (6.4-10.7)	8.9 (5.8-10.9)	8.4 (6.4-10.2)			
	p[b]	0.391	0.382	0.095	0.939	0.119			

[a]Mixed ANOVA: [1] between visits in the same risk group; [2]between low and intermediate risk (main group effect); [3]between low and intermediate risk between visits (measurement x group effect).
[b]Mann-Whitney U test; **p<0.001 and *p=0.001 compared to pretreatment levels (post hoc Bonferroni correction with p<0.005); min: minimum; max: maximum.
SD: Standard deviation; min: minimum; max: maximum.

darbepoetin-treated patients as well as in the low-risk group compared to the intermediate-1-risk group during long-term follow-up.

In this study, the treatment response rates at the 24-month, 36-month, and 48-month visits in the epoetin alfa (43.0%, 33.6%, and 27.1%) and darbepoetin alfa (29.9%, 22.7%, and 16.5%) groups were lower than the 12-month response rates in each group (44.9% and 46.4%, respectively). These findings are consistent with the overall response rates ranging from 20% to 40% and durations of response ranging from 10 to 24 months reported in previous studies on ESAs, considering the refractoriness rate for ESAs to be approximately 40%-50% after 2 years of treatment [6,10,11]. Specifically, multicenter studies of epoetin-treated patients with MDS revealed response rates of approximately 30%-50% with durations of 12-24 months [1,6,15,16,17,18,19,20,21], while single-arm darbepoetin alfa studies reported durations of response ranging from 1 to 36 months [17,22,23,24]. Prospective observational studies also revealed similar response rates for patients treated with epoetin alfa and darbepoetin alfa, despite differences in median response durations obtained with epoetin alfa (7.5-15 months) and darbepoetin alfa (9.7 months) [1,25,26,27].

In addition, in an international pooled analysis of 1698 low-risk MDS patients treated with ESAs, the authors reported that most responses occurred within 3 months, with a median duration of response of 17 months [28]. In a meta-analysis of 10 studies of the efficacy and safety of darbepoetin involving a total of 647 darbepoetin-treated patients, the erythroid response rate was reported to range from 38% to 72% according to the 2000 International Working Group (IWG) criteria, while the response duration was noted to range from 12 months to more than 51 months [29]. Notably, in an epoetin extension study, the median response durations for epoetin alone and for epoetin plus granulocyte colony-stimulating factor were reported to be 34 months and >20 months, respectively [9].

Overall, meta-analyses and systematic reviews have revealed no significant differences in pooled response rates for epoetin alfa and darbepoetin alfa and they have indicated clinical benefits of ESAs, with benefits observed across key clinical outcomes

Table 4. Transfusion needs according to treatment and risk groups.

		Transfusion need, n (%)					
Treatment groups		**Pretreatment**	**12th month**	**24th month**	**36th month**	**48th month**	**p[1]**
Epoetin alfa	Yes	43 (40.2)	15 (16.1)**	14 (13.5)**	13 (14.3)**	9 (11.8)**	**<0.001**
	No	64 (59.8)	78 (83.9)	90 (86.5)	78 (85.7)	67 (88.2)	
Darbepoetin alfa	Yes	37 (38.1)	17 (18.7)	27 (29)	19 (22.9)	18 (25)	**0.004**
	No	60 (61.9)	74 (81.3)	66 (71)	64 (77.1)	54 (75)	
p (e. alfa vs. d. alfa)		0.765[2]	0.793[3]	0.012[3]	0.205[3]	0.063[3]	-
Risk groups		**Pretreatment**	**12th month**	**24th month**	**36th month**	**48th month**	**p[1]**
Low risk	Yes	51 (34)	20 (15.4)*	24 (16.4)*	18 (14.1)**	13 (11.7)**	**<0.001**
	No	99 (66)	110 (84.6)	122 (83.6)	110 (85.9)	98 (88.3)	
Intermediate-1 risk	Yes	29 (53.7)	12 (22.2)	17 (33.3)	14 (30.4)	14 (37.8)	**0.005**
	No	25 (46.3)	42 (77.8)	34 (66.7)	32 (69.6)	23 (62.2)	
p (low vs. int-1 risk)		**0.011[2]**	0.368[3]	**0.018[3]**	**0.025[3]**	**<0.001[3]**	-

[1]Cochran's Q test, [2]chi-square test, [3]continuity correction.
*p<0.01 and **p<0.001 compared to baseline pretreatment transfusion needs (McNemar test with Bonferroni correction, p<0.005).

Table 5. Treatment response (≥1.5 g/dL increase in hemoglobin) rates from baseline and from the previous visit during long-term follow-up.

	Percentage of patients with increase of at least 1.5 g/dL in hemoglobin levels								
	12th month	**24th month**		**36th month**		**48th month**		**p[1]**	
	vs. baseline	vs. baseline	vs. previous visit	vs. baseline	vs. previous visit	vs. baseline	vs. previous visit	vs. baseline	vs. previous visit
Treatment groups									
Epoetin alfa	48 (44.9)	46 (43.0)	10 (9.3)	36 (33.6)***	6 (5.6)	29 (27.1)**[q]	4 (3.7)	0.002	0.229
Darbepoetin alfa	45 (46.4)	29 (29.9)	10 (10.3)	22 (22.7)	5 (5.2)	16 (16.5)***	1 (1.0)[w]	<0.001	0.017
p[2] (e. alfa vs. d. alfa)	0.826[2]	0.073[3]	1.00[3]	0.114[3]	1.00[3]	0.098[3]	0.372[4]		
Risk groups									
Low risk	69 (46.0)	59 (39.3)	14 (9.3)	45 (30.0)**	9 (6.0)	39 (26.0)***	5 (3.3)	<0.001	0.096
Intermediate risk	24 (44.4)	16 (29.6)	6 (11.1)	13 (24.1)*	2 (3.7)	6 (11.1)***[q]	0 (0.0)[w]	<0.001	0.030
p[2] (low vs. int-1 risk)	0.184	0.270[3]	0.913[3]	0.513[3]	0.731[4]	0.038[2]	0.328[4]		

[1]Cochran's Q test; [2]chi-square test; [3]Yates continuity correction; [4]Fisher exact test.
*p<0.05 and **p<0.001 compared to 12th month; [q] p<0.01 compared to 24th month, [w]p<0.05 compared to increase from previous visit at 24th month (McNemar test with Bonferroni correction, p<0.05).

(improved erythroid response rates and duration of response), as well as reduction in transfusion needs [1,30,31,32].

Our previous study involving the interim analysis of 12-month results indicated the similar efficacy of epoetin alfa and darbepoetin alfa among low-risk and intermediate-1-risk MDS patients with no differences in treatment responses between the treatment groups (12-month response rates: 58.1% for epoetin alfa and 41.9% for darbepoetin alfa), whereas the likelihood of earlier treatment response (within the first 3 months: 62.7%) and achievement of an earlier reduction in transfusion needs was noted in the epoetin alfa group [12]. In the current extension study, while the two treatment groups had similar efficacy in terms of rates and durations of treatment responses for up to 48 months of follow-up, the epoetin-treated patients had a slower decrease in treatment response from baseline along with significantly higher hemoglobin levels accompanied by a greater reduction in transfusion needs from 24 to 48 months of follow-up.

In a meta-analysis of 55 studies, transfusion independence was concluded to be associated with decreased mortality (hazard ratio: 0.41; 95% confidence interval: 0.29-0.56) [33]. Hence, the increased likelihood of transfusion independency with long-term epoetin treatment and lower-risk MDS in our cohort seems to be particularly notable given that the primary target in managing patients with lower-risk MDS in daily practice is to achieve transfusion independence, which is associated with improved survival [6,15,20,33,34,35]. Indeed, epoetin alfa treatment for patients with MDS is considered likely to achieve

durable responses, thereby guaranteeing an improvement in the quality of life for these patients [10].

In a retrospective cohort study of 36 patients diagnosed with MDS and treated with epoetin alfa (30,000 to 60,000 IU per week), the authors reported a response rate of 80.5% with surprisingly prolonged responses (range: 25-175 months) in 82.8% of patients, who were also transfusion-independent and had favorable response stratifications [10]. Hemoglobin values were reported to increase significantly after 24 months and up to 175 months after the initiation of epoetin alfa treatment, and they remained above the baseline values, while the overall survival rate was 51.64% after a median of 65 months of treatment along with 43.5-month median event-free survival [10]. The authors indicated an association of epoetin alfa with higher overall survival and event-free survival rates and longer response durations in their study than previously described in the literature, and they emphasized that the likelihood of sustained rates of erythroid response following the initiation of epoetin alfa treatment also reflected the need for prolonged treatment to obtain the full clinical benefits [10].

The factors associated with treatment response in ESA-treated MDS patients have been reported to include certain clinical characteristics such as low serum EPO levels, a lack of transfusion dependence, and a low-risk stratification based on the Revised International Prognostic Scoring System [5,29,32,36]. In particular, high-risk stratifications and transfusion dependence, in relation to their negative impact on event-free survival, are considered likely to be predictors of poor response to epoetin alfa treatment [10]. The association of epoetin alfa versus darbepoetin alfa treatment as well as low-risk versus intermediate-1-risk status with significantly higher hemoglobin levels and greater decrease in transfusion dependency in the current study supports the previously reported data on lower rates and shorter durations of response to epoetin treatment in high-risk MDS patients and those with transfusion dependence [10,37]. Indeed, treatment with ESAs has been associated with delays in transfusion needs along with substantial increases in hemoglobin levels for longer periods of time [10]. The increased likelihood of erythroid response with a longer duration of ESA treatment among later responders has also been suggested together with the potential benefit of continuing ESA administration even after a lack of treatment response within the initial 8 to 12 weeks [7,36,38].

The dose-dependency of ESA efficacy has also been emphasized with the consideration of epoetin at 60,000 U/week and darbepoetin at 300 µg/week as being superior to lower doses [11,35,39], while more frequent dosing and prolonged treatment are considered to be necessary to obtain the full clinical benefit [29,35,38]. In addition, the implementation of the stringent 2006 IWG criteria (1.5 g/dL hemoglobin increase maintained for 8 weeks, even in patients with low transfusion burdens) is considered likely to yield a lower-than-expected clinical benefit rate [35]. An increase in the observed response rates with ESAs was reported after relaxing the strict interpretation of the 2006 IWG criteria, with these rates shifting from 15% to 24% in the ARCADE study and from 32% to 46% in EPOANE3021 [1,18,35], as well as in other ESA studies using other erythroid response criteria [1,40,41]. Moreover, early dose reduction for patients with a rapid hemoglobin rise who are still anemic is suggested to hamper the achievement of sustained hemoglobin responses and thus to lower the erythroid response rate [1]. Nonetheless, the recently proposed revised IWG criteria for assessment of hematologic response include the requirement that the duration of hematologic improvement last 16 weeks (versus 8 weeks), among other recommendations [11,42].

Importantly, given the occurrence of functional changes in hormonal receptors upon chronic exposure to agonists and that ESAs are used for the long-term treatment of anemia, gradual decreases in responses to ESAs after 24 months could also be a result of the downregulation of EPO receptors after prolonged exposure to ESAs or may be related to disease progression [43,44,45].

Study Limitations

Certain limitations to this study should be considered. First, due to the retrospective design, establishing temporality between cause and effect is not possible. Second, the lack of data on the timing of ESA initiation and the use of patient-reported outcome measures related to quality of life are other limitations. Further data on these points would extend the knowledge achieved in the current study.

Conclusion

This real-life long-term ESA extension study investigated the clinical efficacy of epoetin alfa and darbepoetin alfa for up to 48 months and revealed that treatment efficacy reached a plateau starting from the 24th month of therapy with a continuing decrease in treatment response rates regardless of treatment type, risk status, or gender. Nonetheless, significantly higher hemoglobin levels and marked improvement in transfusion needs were noted among epoetin-treated patients compared to darbepoetin-treated patients and in the low-risk group compared to the intermediate-1-risk group. These findings emphasize the likelihood of long-term epoetin treatment achieving a durable reduction in transfusion needs and a substantial increase in hemoglobin levels for longer periods by delaying the need for transfusions and thus increasing the probability of improved quality of life and prolonged survival for low-risk MDS patients.

Ethics

Ethics Committee Approval: This study was approved by the Zonguldak Bülent Ecevit University Clinical Research Ethics

Committee (date of approval: 01/12/2021; reference number/ protocol no: 2021/23).

Informed Consent: Written informed consent was obtained from all patients.

Authorship Contributions

Concept: M.A.A., Ş.E.; Data Collection or Processing: M.A.A., A.G., İ.H.A., C.S.; Analysis or Interpretation: M.G.P., İ.H.A., C.S.; Literature Search: M.A.A., A.G., İ.H.A., M.G.P., C.S., T.H.; Writing: Ş.E., A.Z.B., B.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Park S, Greenberg P, Yucel A, Farmer C, O'Neill F, De Oliveira Brandao C, Fenaux P. Clinical effectiveness and safety of erythropoietin-stimulating agents for the treatment of low- and intermediate-1-risk myelodysplastic syndrome: a systematic literature review. Br J Haematol 2019;184:134-160.
2. Malcovati L, Hellström-Lindberg E, Bowen D, Adès L, Cermak J, Del Cañizo C, Della Porta MG, Fenaux P, Gattermann N, Germing U, Jansen JH, Mittelman M, Mufti G, Platzbecker U, Sanz GF, Selleslag D, Skov-Holm M, Stauder R, Symeonidis A, van de Loosdrecht AA, de Witte T, Cazzola M; European LeukemiaNet. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood 2013;122:2943-2964.
3. Fenaux P, Haase D, Sanz GF, Santini V, Buske C; ESMO Guidelines Working Group. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3):57-69.
4. Killick SB, Carter C, Culligan D, Dalley C, Das-Gupta E, Drummond M, Enright H, Jones GL, Kell J, Mills J, Mufti G, Parker J, Raj K, Sternberg A, Vyas P, Bowen D; British Committee for Standards in Haematology. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. Br J Haematol 2014;164:503-525.
5. Park S, Kelaidi C, Sapena R, Vassilieff D, Beyne-Rauzy O, Coiteux V, Vey N, Ravoet C, Cheze S, Rose C, Legros L, Stamatoullas A, Escoffre-Barbe M, Guerci A, Chaury MP, Fenaux P, Dreyfus F. Early introduction of ESA in low risk MDS patients may delay the need for RBC transfusion: a retrospective analysis on 112 patients. Leuk Res 2010;34:1430-1436.
6. Park S, Kelaidi C, Sapena R, Vassilieff D, Beyne-Rauzy O, Coiteux V, Vey N, Ravoet C, Cheze S, Rose C, Legros L, Stamatoullas A, Escoffre-Barbe M, Guerci A, Chaury MP, Fenaux P, Dreyfus F. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood 2008;111:574-582.
7. Duong VH, Baer MR, Hendrick F, Weiss SR, Sato M, Zeidan AM, Gore SD, Davidoff AJ. Variations in erythropoiesis-stimulating agent administration in transfusion-dependent myelodysplastic syndromes impact response. Leuk Res 2015;39:586-591.
8. Greenberg PL, Attar E, Bennett JM, Bloomfield CD, Borate U, De Castro CM, Deeg HJ, Frankfurt O, Gaensler K, Garcia-Manero G, Gore SD, Head D, Komrokji R, Maness LJ, Millenson M, O'Donnell MR, Shami PJ, Stein BL, Stone RM, Thompson JE, Westervelt P, Wheeler B, Shead DA, Naganuma M. Myelodysplastic syndromes: clinical practice guidelines in oncology. J Natl Compr Canc Netw 2013;11:838-874.
9. Negrin RS, Stein R, Doherty K, Cornwell J, Vardiman J, Krantz S, Greenberg PL. Maintenance treatment of the anemia of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor and erythropoietin: evidence for in vivo synergy. Blood 1996;87:4076-4081.
10. Moura ATG, Duarte FB, Barbosa MC, Santos TEJD, Lemes RPG. Prolonged response to recombinant human erythropoietin treatment in patients with myelodysplastic syndrome at a single referral centre in Brazil. Clinics (Sao Paulo) 2019;74:e771.
11. Carraway HE, Saygin C. Therapy for lower-risk MDS. Hematology Am Soc Hematol Educ Program. 2020;2020:426-433.
12. Ak MA, Sahip B, Geduk A, Ucar MA, Kale H, Hacibekiroglu T, Polat MG, Kalpakci Y, Bolaman AZ, Guvenc B, Ertop S. The clinical efficacy of epoetin alfa and darbepoetin alfa in patients with low-risk or intermediate-1-risk myelodysplastic syndrome: retrospective multi-center real-life study. Indian J Hematol Blood Transfus 2022;38:299-308.
13. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, Sanz M, Vallespi T, Hamblin T, Oscier D, Ohyashiki K, Toyama K, Aul C, Mufti G, Bennett J. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088.
14. Tefferi A, Barosi G, Mesa RA, Cervantes F, Deeg HJ, Reilly JT, Verstovsek S, Dupriez B, Silver RT, Odenike O, Cortes J, Wadleigh M, Solberg LA Jr, Camoriano JK, Gisslinger H, Noel P, Thiele J, Vardiman JW, Hoffman R, Cross NC, Gilliland DG, Kantarjian H; IWG for Myelofibrosis Research and Treatment (IWG-MRT). International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). Blood 2006;108:1497-1503.
15. Jädersten M, Malcovati L, Dybedal I, Della Porta MG, Invernizzi R, Montgomery SM, Pascutto C, Porwit A, Cazzola M, Hellström-Lindberg E. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. J Clin Oncol 2008;26:3607-3613.
16. Ross SD, Allen IE, Probst CA, Sercus B, Crean SM, Ranganathan G. Efficacy and safety of erythropoiesis-stimulating proteins in myelodysplastic syndrome: a systematic review and meta-analysis. Oncologist 2007;12:1264-1273.
17. Kelaidi C, Beyne-Rauzy O, Braun T, Sapena R, Cougoul P, Adès L, Pillard F, Lamberto C, Charniot JC, Guerci A, Choufi B, Stamatoullas A, Slama B, De Renzis B, Ame S, Damaj G, Boyer F, Chaury MP, Legros L, Cheze S, Testu A, Gyan E, Béné MC, Rose C, Dreyfus F, Fenaux P. High response rate and improved exercise capacity and quality of life with a new regimen of darbepoetin alfa with or without filgrastim in lower-risk myelodysplastic syndromes: a phase II study by the GFM. Ann Hematol 2013;92:621-631.
18. Fenaux P, Santini V, Spiriti MAA, Giagounidis A, Schlag R, Radinoff A, Gercheva-Kyuchukova L, Anagnostopoulos A, Oliva EN, Symeonidis A, Berger MH, Götze KS, Potamianou A, Haralampiev H, Wapenaar R, Milionis I, Platzbecker U. A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin-α in anemic patients with low-risk MDS. Leukemia 2018;32:2648-2658.
19. Spiriti MA, Latagliata R, Niscola P, Cortelezzi A, Francesconi M, Ferrari D, Volpe E, Clavio M, Grossi A, Reyes MT, Musto P, Mitra ME, Azzarà A, Pagnini D, D'Arena G, Spadano A, Balleari E, Pecorari P, Capochiani E, De Biasi E, Perego D, Monarca B, Pisani F, Scaramella G, Petti MC. Impact of a new dosing regimen of epoetin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome. Ann Hematol 2005;84:167-176.
20. Greenberg PL, Sun Z, Miller KB, Bennett JM, Tallman MS, Dewald G, Paietta E, van der Jagt R, Houston J, Thomas ML, Cella D, Rowe JM. Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996). Blood 2009;114:2393-2400.
21. Musto P, Villani O, Martorelli MC, Pietrantuono G, Guariglia R, Mansueto G, D'Auria F, Grieco V, Bianchino G, Sparano A, Zonno A, Lerose R, Sanpaolo G, Falcone A. Response to recombinant erythropoietin alpha, without

the adjunct of granulocyte-colony stimulating factor, is associated with a longer survival in patients with transfusion-dependent myelodysplastic syndromes. Leuk Res 2010;34:981-985.

22. Gotlib J, Lavori P, Quesada S, Stein RS, Shahnia S, Greenberg PL. A phase II intra-patient dose-escalation trial of weight-based darbepoetin alfa with or without granulocyte-colony stimulating factor in myelodysplastic syndromes. Am J Hematol 2009;84:15-20.
23. Mannone L, Gardin C, Quarre MC, Bernard JF, Vassilieff D, Ades L, Park S, Vaultier S, Hamza F, Beyne-Rauzy MO, Cheze S, Giraudier S, Agape P, Legros L, Voillat L, Dreyfus F, Fenaux P; Groupe Francais des Myelodysplasies. High-dose darbepoetin alpha in the treatment of anaemia of lower risk myelodysplastic syndrome results of a phase II study. Br J Haematol 2006;133:513-519.
24. Oliva EN, Nobile F, Alimena G, Specchia G, Danova M, Rovati B, Ronco F, Impera S, Risitano A, Alati C, Breccia M, Carmosino I, Vincelli I, Latagliata R. Darbepoetin alfa for the treatment of anemia associated with myelodysplastic syndromes: efficacy and quality of life. Leuk Lymphoma 2010;51:1007-1014.
25. Sekeres MA, Schoonen WM, Kantarjian H, List A, Fryzek J, Paquette R, Maciejewski JP. Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. J Natl Cancer Inst 2008;100:1542-1551.
26. Pierri I, Balleari E, Olcese E, Passalia C, Calvia A, Clavio M, Varaldo R, Miglino M, Ballerini F, Canepa L, Ghiggi C, Vignolo L, Ghiso A, Ghio R, Gobbi M. High dose of r-EPO (40,000 IU) once a week is highly effective in a selected cohort of MDS patients with basal EPO level < 250mu/mi, IPSS score ≤ 1.5 and low transfusional need [abstract]. Leuk Res 2007;31:S140.
27. Mele G, Musto C, Matera R, Vigliotti ML, Tartarone A, Romano G, Coccaro MR, Di Renzo N. High-dose of epoetin alfa in patients with low-risk myelodysplastic syndromes (MDS): a single institution experience. Blood 2004;104:260B.
28. Park S, Hamel JF, Toma A, Kelaidi C, Thépot S, Campelo MD, Santini V, Sekeres MA, Balleari E, Kaivers J, Sapena R, Götze K, Müller-Thomas C, Beyne-Rauzy O, Stamatoullas A, Kotsianidis I, Komrokji R, Steensma DP, Fensterl J, Roboz GJ, Bernal T, Ramos F, Calabuig M, Guerci-Bresler A, Bordessoule D, Cony-Makhoul P, Cheze S, Wattel E, Rose C, Vey N, Gioia D, Ferrero D, Gaidano G, Cametti G, Pane F, Sanna A, Germing U, Sanz GF, Dreyfus F, Fenaux P. Outcome of lower-risk patients with myelodysplastic syndromes without 5q deletion after failure of erythropoiesis-stimulating agents. J Clin Oncol 2017;35:1591-1597.
29. Park S, Fenaux P, Greenberg P, Mehta B, Callaghan F, Kim C, Tomita D, Xu H. Efficacy and safety of darbepoetin alpha in patients with myelodysplastic syndromes: a systematic review and meta-analysis. Br J Haematol 2016;174:730-747.
30. Gascón P, Krendyukov A, Mathieson N, Aapro M. Epoetin alfa for the treatment of myelodysplastic syndrome-related anemia: a review of clinical data, clinical guidelines, and treatment protocols. Leuk Res 2019;81:35-42.
31. Moyo V, Lefebvre P, Duh MS, Yektashenas B, Mundle S. Erythropoiesis-stimulating agents in the treatment of anemia in myelodysplastic syndromes: a meta-analysis. Ann Hematol 2008;87:527-536.
32. Velloso EDRP, Magalhães SMM, Chauffaille MLLF, Buzzini R, Bernardo WM. Part 3: Myelodysplastic syndromes—Treatment of low-risk patients without the 5q deletion. Hematol Transfus Cell Ther 2018;40:267-273.
33. Harnan S, Ren S, Gomersall T, Everson-Hock ES, Sutton A, Dhanasiri S, Kulasekararaj A. Association between transfusion status and overall survival in patients with myelodysplastic syndromes: a systematic literature review and meta-analysis. Acta Haematol 2016;136:23-42.
34. Symeonidis A, Zikos P, Galanopoulos A, Kotsianidis I, Kouraklis A, Protopapa M, Psyllaki M, Lambropoulou V, Aktypi A, Bakarakos P, TSatalas C. Response to treatment with erythropoietin in patients with MDS highly predicts low risk of evolution to AML and longer survival. Leuk Res 2011;35:S127-128.
35. Platzbecker U, Symeonidis A, Oliva EN, Goede JS, Delforge M, Mayer J, Slama B, Badre S, Gasal E, Mehta B, Franklin J. A phase 3 randomized placebo-controlled trial of darbepoetin alfa in patients with anemia and lower-risk myelodysplastic syndromes. Leukemia 2017;31:1944-1950.
36. Santini V. Clinical use of erythropoietic stimulating agents in myelodysplastic syndromes. Oncologist 2011;16(Suppl 3):35-42.
37. Hellström-Lindberg E, Malcovati L. Supportive care, growth factors, and new therapies in myelodysplastic syndromes. Blood Rev 2008;22:75-91.
38. Terpos E, Mougiou A, Kouraklis A, Chatzivassili A, Michalis E, Giannakoulas N, Manioudaki E, Lazaridou A, Bakaloudi V, Protopappa M, Liapi D, Grouzi E, Parharidou A, Symeonidis A, Kokkini G, Laoutaris NP, Vaipoulos G, Anagnostopoulos NI, Christakis JI, Meletis J, Bourantas KL, Zoumbos NC, Yataganas X, Viniou NA; Greek MDS Study Group. Prolonged administration of erythropoietin increases erythroid response rate in myelodysplastic syndromes: a phase II trial in 281 patients. Br J Haematol 2002;118:174-180.
39. Hellström-Lindberg E, Ahlgren T, Beguin Y, Carlsson M, Carneskog J, Dahl IM, Dybedal I, Grimfors G, Kanter-Lewensohn L, Linder O, Luthman M, Löfvenberg E, Nilsson-Ehle H, Samuelsson J, Tangen JM, Winqvist I, Oberg G, Osterborg A, Ost A. Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. Blood 1998;92:68-75.
40. Buckstein R, Balleari E, Wells R, Santini V, Sanna A, Salvetti C, Crisà E, Allione B, Danise P, Finelli C, Clavio M, Poloni A, Salvi F, Cilloni D, Oliva EN, Musto P, Houston B, Zhu N, Geddes M, Leitch H, Leber B, Sabloff M, Nevill TJ, Yee KW, Storring JM, Francis J, Maurillo L, Latagliata R, Spiriti MAA, Andriani A, Piccioni AL, Fianchi L, Fenu S, Gumenyuk S, Buccisano F. ITACA: A new validated international erythropoietic stimulating agent-response score that further refines the predictive power of previous scoring systems. Am J Hematol 2017;92:1037-1046.
41. Houston BL, Jayakar J, Wells RA, Lenis M, Zhang L, Zhu N, Leitch HA, Nevill TJ, Yee KWL, Leber B, Sabloff M, St-Hilaire E, Kumar R, Geddes M, Shamy A, Storring JM, Keating MM, Elemary M, Delage R, Mamedov A, Buckstein R. A predictive model of response to erythropoietin stimulating agents in myelodysplastic syndrome: from the Canadian MDS patient registry. Ann Hematol 2017;96:2025-2029.
42. Platzbecker U, Fenaux P, Adès L, Giagounidis A, Santini V, van de Loosdrecht AA, Bowen D, de Witte T, Garcia-Manero G, Hellström-Lindberg E, Germing U, Stauder R, Malcovati L, Sekeres MA, Steensma DP, Gloaguen S. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. Blood 2019;133:1020-1030.
43. Trincavelli ML, Da Pozzo E, Ciampi O, Cuboni S, Daniele S, Abbracchio MP, Martini C. Regulation of erythropoietin receptor activity in endothelial cells by different erythropoietin (EPO) derivatives: an in vitro study. Int J Mol Sci 2013;14:2258-2281.
44. Choi MJ, Yee J. Erythropoiesis-stimulating agents and cancer: myth or truth. Adv Chronic Kidney Dis 2019;26:221-224.
45. Hedley BD, Allan AL, Xenocostas A. The role of erythropoietin and erythropoiesis-stimulating agents in tumor progression. Clin Cancer Res 2011;17:6373-6380.