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REVIEW ARTICLE

Erythropoiesis-stimulating agents in the treatment of anemia in myelodysplastic syndromes: a meta-analysis

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Abstract The present meta-analysis was undertaken to (1) assess erythroid response rates in myelodysplastic syndromes (MDS) patients treated with epoetin alfa as a monotherapy, (2) gain further insights into predictors of response rates, and (3) compare the erythroid response rates observed with epoetin alfa and darbepoetin alfa. A systematic review of studies from 1990 to 2006 in MDS patients treated with epoetin alfa or darbepoetin alfa was performed and yielded 30 studies evaluating a total of 1,314 patients (epoetin alfa: 22 studies, 925 patients; darbepoetin alfa: eight studies, 389 patients). Pooled estimates of erythroid response rates, stratified by the International Working Group criteria (IWGc) and treatment group, were calculated using random-effects meta-analysis methods. Univariate meta-regression analyses were further conducted to identify study characteristics associated with erythroid response rate. The pooled estimate of erythroid response rate was significantly higher for epoetin alfa IWGc studies (57.6%) as compared to non-IWGc studies (31.6%; $p<0.001$). Study factors predictive of higher response rate in the epoetin alfa IWGc studies included higher proportion of patients with RA/RARS ($p<0.001$), lower mean baseline serum erythropoietin level ($p=0.007$), and fixed dosing regimen ($p<0.001$). There was no significant difference in the pooled erythroid response rates between the two agents (epoetin alfa: 57.6% vs. darbepoetin alfa: 59.4%; $p=0.828$). The current study reported significantly higher erythroid response rates predominantly in the more recent studies that primarily utilized IWGc to define response. With the use of standardized patient selection and response evaluation methods, epoetin alfa and darbepoetin alfa yielded comparable erythroid response rates in MDS patients.

Keywords Anemia · Myelodysplastic syndromes (MDS) · Epoetin alfa · Darbepoetin alfa · Erythropoietic stimulating therapies (ESAs) · Meta-analysis

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Introduction

Myelodysplastic syndromes (MDS) represent a heterogeneous group of clonal bone marrow stem cell disorders characterized by abnormal proliferation and differentiation of hematopoietic precursors resulting in ineffective hematopoiesis, refractory cytopenias, and a propensity to evolve into acute myeloid leukemia (AML) [1–3].

Patient prognosis and risk of progression to AML can be predicted by the International Prognostic Scoring System (IPSS) for MDS, which is based on the presence or absence of multilineage cytopenias, abnormal marrow cytogenetics, and increased marrow blast counts [4]. The only curative option is allogeneic hematopoietic stem cell transplantation. However, this procedure is limited by donor availability and significant toxicity, especially in the older population,

which MDS commonly afflicts. Furthermore, for patients with low or intermediate-1 IPSS scores, several other approaches than hematopoietic transplantation are preferred [5]. Secondly, most patients in the lower risk categories die from causes other than leukemia [6]. In these patients, the course of disease is marked by prolonged survival with chronic cytopenias and infrequent evolution to AML. As such, for a great majority of MDS patients, the goal of disease management is to treat the complications of cytopenia with supportive care for anemia and thrombocytopenia, and antimicrobial therapy for infectious complications. Furthermore, for this largely incurable disease, improving quality of life is an important goal [7].

Anemia, the clinical hallmark of this disease, is present in up to 80–85% of MDS patients at diagnosis, and may also develop during the course of the disease, often necessitating blood transfusions [1]. Unfortunately, repeated transfusions of red blood cells are associated with infectious complications, iron overload, and more importantly, appear to be associated with decreased survival and leukemic evolution in patients with MDS, although that finding might be confounded with worse underlying health status in patients requiring transfusions [6]. Furthermore, transfusion therapy places great strain on the limited donor blood supply, which faces daily challenges of collection, processing, and distribution [8–10].

Recombinant human erythropoietin (epoetin alfa), administered either alone or in combination with granulocyte or granulocyte–macrophage colony-stimulating factors (G-CSF or GM-CSF), has been extensively studied as a means to improve erythropoiesis [11] and reduce red blood cell transfusions in MDS patients with anemia [12–14].

Historically, the use of epoetin alfa in patients with MDS from heterogeneous populations, and more importantly, the absence of standardized response evaluation methods, led to a tremendous variability in reported erythroid response rates to epoetin alfa monotherapy in published literature. In the late 1990s, it was found that patients with low to intermediate-1 (INT-1) disease with low transfusion requirements and lower endogenous serum erythropoietin levels may show the best response to epoetin alfa and thus may be better candidates for erythropoietic therapy [15–17]. Recently, another erythropoiesis-stimulating agent (ESA), darbepoetin alfa, has also been shown to be effective in the treatment of MDS-related anemia [18–20]. In 2000, the International Working Group conducted a review of currently used response definitions and introduced a uniform set of criteria for assessing response in future clinical trials in MDS [7]. These standardized criteria were developed in an effort to improve communication among investigators and to allow comparability among clinical trials. The advent of the International Working Group criteria (IWGc), and revision in 2006, should better enable the comparison of erythroid response rates to erythropoietic therapy [7].

The purpose of the present meta-analysis was: (1) to assess erythroid response rates in MDS patients treated with epoetin alfa as a monotherapy in studies that did and did not use the IWGc, (2) to gain further insights into predictors of response rates, and (3) to compare the erythroid response rates observed with epoetin alfa and darbepoetin alfa when adjusted for the IWGc.

Materials and methods

Literature search

A systematic search of the medical literature was conducted for studies of epoetin alfa or darbepoetin alfa in patients with MDS for the period 1990 to 2006 using the PubMed database. The search was performed using the following keywords: “epoetin alfa or rHuEPO or darbepoetin alfa or novel erythropoiesis stimulating protein” & “myelodysplastic syndromes”. An additional search for abstracts from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) proceedings was also conducted. Results of the search were initially analyzed in title and abstract format. Reference sections from the selected publications were checked for additional articles or abstracts. Items were selected based on an initial search for a full-text analysis to determine the eligibility of the article for our analysis.

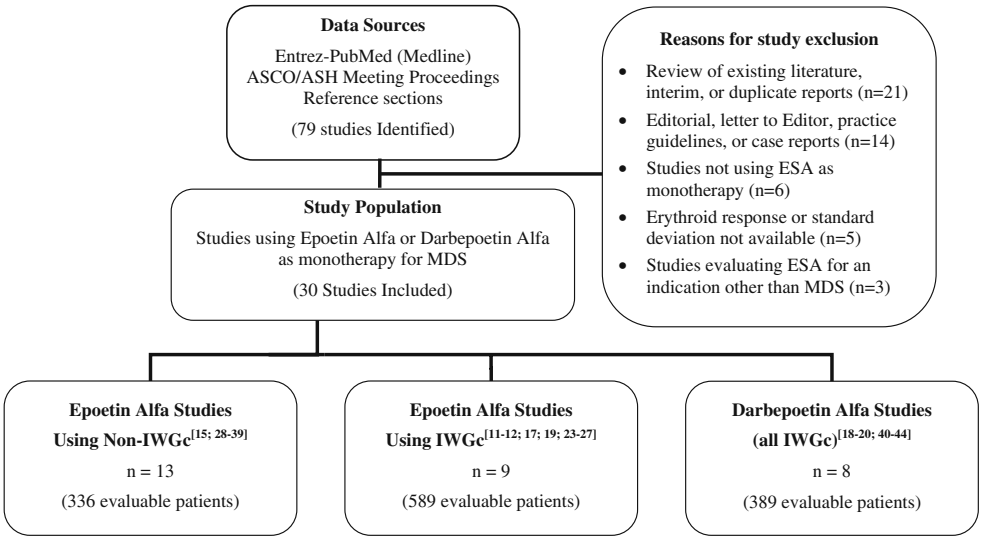
Criteria for inclusion of studies for analysis

All studies and abstracts that evaluated the effectiveness of epoetin alfa or darbepoetin alfa as a monotherapy for the treatment of MDS-related anemia were included. The only additional criterion applied was the availability of erythroid response to assess treatment effectiveness in patients naive to erythropoietic treatment. Studies reported in languages other than English were included in this review if the relevant data for the analysis were available from the abstract. Figure 1 summarizes the study disposition.

Data extraction

Two reviewers independently assessed the quality of the data collected using a standardized methodology. Each reviewer evaluated relevant data from the eligible studies and entered the information electronically into a Microsoft Excel data collection form with pre-specified fields. If relevant data were reported only graphically, values were estimated by measuring the charts. Quality control was done by comparing the two independent datasets and any

Fig. 1 Study disposition



differences were reconciled by a third party, referring to the original sources.

Information regarding the study design and outcomes were collected for each included study. This included the number of patients enrolled, relevant aspects of study design (e.g., definition of erythroid response), baseline characteristics of patients, dosing regimen, and erythroid response rate.

Analytical approach

Studies included in the analysis were stratified by the use or non-use of IWGc erythroid response definition and by treatment group. An attempt was made to recalculate response rates in non-IWGc studies according to the IWGc definition; however, the non-IWGc studies did not provide enough detailed information to reconcile the data. For this reason, in the first objective, epoetin alfa studies using IWGc to define erythroid response were compared to epoetin alfa studies using a different definition of erythroid response (non-IWGc studies). For the second objective, univariate meta-regression analysis was performed using epoetin alfa IWGc studies to identify the potential baseline predictors for response rate. For the third objective, response rates between epoetin alfa and darbepoetin alfa were compared when adjusted for the IWGc. Since all darbepoetin alfa studies included in the analysis used IWGc to define erythroid response, this comparison was based solely on epoetin alfa studies also utilizing IWGc. Since none of the studies used the recent modified IWGc criteria [21], only the original IWGc criteria were used as described below [7].

Erythroid response rate was the outcome measure for these meta-analyses. For IWGc studies, erythroid response was defined as major (i.e., increase of >2 g/dL in Hb level from baseline in patients with a hemoglobin of ≤11g/dL or transfusion independence for transfusion-dependent patients) plus minor (i.e., increase of 1–2 g/dL in Hb level from baseline in patients with a hemoglobin of ≤11 g/dL or 50% reduction in transfusion requirements for transfusion-dependent patients). For the non-IWGc studies, hematologic response rate definitions were variable and included: favorable response, complete response, and partial response (Table 1).

Univariate baseline statistics were generated for epoetin alfa and darbepoetin alfa studies. Frequency counts and percentages were used to summarize categorical variables while means and standard deviations were used for continuous variables. Statistical comparisons between groups were conducted using chi-square tests for categorical variables and two-sided Student's *t* tests for continuous variables.

Meta-analysis

Pooled estimates of erythroid response rates and 95% confidence intervals (CI) were calculated and plotted for each group using random-effects meta-analysis methods [22]. Under the random-effects model, it is assumed that in addition to variability within studies, there is also variability among studies. This among-study variability was assessed using the I-squared statistic (i.e., variation attributable to heterogeneity) and tested by the heterogeneity test where a low p value implies that the study results are heterogeneous and a random-effects model, instead of a fixed-effects model is more appropriate. In addition, univariate meta-regression analyses were conducted, with supplemental descriptive statistics, to identify study char-

Table 1 Erythroid response definitions by study for non-IWGc studies

Study name	Response term(s)	Response description
Stein (1991)	Response	≥4% point increase in hematocrit (Hct) from baseline (BL) in the absence of transfusions or maintenance of Hct level from BL and elimination of transfusions
Adamson (1992)	Response	Reducing (>50%) or eliminating transfusion requirements, or showing an improvement in hematocrit of ≥6%
Rafanelli (1992)	Complete	Stable, non-transfusion supported increase of ≥1 g/dL
	Partial	50% decrease in transfusions
Verhoef (1992)	Response	1 g/dL increase in Hb after 4 weeks in the absence of transfusions ±30% decrease in monthly transfusion requirements vs. monthly transfusion requirements at BL
Aloe Spiriti (1993)	Complete	Normalization of Hb levels lasting 3 months
	Partial	Stable increase in Hb ≥1 g/dL ±50% decrease in transfusion requirements
	Resistant to therapy	Unmodified Hb levels or <50% decrease in transfusion requirements
Goy (1993)	Response	Hb increase between 9 and 11 g/dL in the absence of transfusions or a 30% decrease in average transfusion requirements (RBC units/week) vs. transfusion requirements from 3 months before epoetin alfa treatment
Ludwig (1993)	Response	≥2 g/dL increase in Hb (1.24 mmol/L) in the absence of transfusions (patients must be totally transfusion independent, Hb values 2 weeks after transfusion are eliminated)
Stenke (1993)	Response	Hb increase ≥15 to 105 g/L or transfusion independence
Zeigler (1993)	Response	>2 g/dL increase in Hb or 50% decrease in transfusion requirements
Marques da Costa (1994)	Response	≥1 g/dL increase in Hb or decrease in transfusion needs of over 50%
Rose (1995)	Hct response	6% increase in Hct in the absence of transfusions 1 month prior
	Transfusion response	50% decrease in transfusions during the last 12 weeks
Wallvik (2002)	Response	Hb increase ≥15 to 105 g/L or transfusion independence
Tsabouri (2004)	Response	Complete loss of transfusion requirement or increase of the Hb level by more than 2 g/dL if transfusion was not required

acteristics that were significant determinants of erythroid response rate using epoetin alfa IWGc studies.

A two-sided alpha error of 0.05 was used to declare statistical significance. All statistical analyses were performed using SAS release 9.1 or newer (SAS Institute, Inc., Cary, NC, USA) or Intercooled Stata 9.0 software.

Results

Selection of studies

The initial search yielded 79 studies from Medline, ASCO/ASH meeting proceedings, or the references sections of identified Medline publications. A total of 30 studies [11, 12, 15, 17–20, 23–44] were included in the current analysis (Fig. 1). Reviews of existing literature, interim or duplicate reports (n=21), and editorials, letters to the editor, practice guidelines, or case reports (n=14) were excluded. In addition, studies not using ESA as monotherapy (n=6), those for which erythroid response rate or standard deviation were not available (n=5), and studies evaluating erythropoietic agents for an indication other than MDS (n=3) were also excluded. The remaining study set included 22 unique epoetin alfa studies with non-overlapping patient populations (13 non-IWGc and nine IWGc studies) and eight studies using darbepoetin alfa (all IWGc studies).

Erythroid response to epoetin alfa monotherapy

A total of 925 patients receiving epoetin alfa were evaluable for erythroid response (589 IWGc and 336 non-IWGc). Table 2 describes the baseline characteristics for those patients evaluated for response using non-IWGc vs. IWGc. Of note, the proportion of transfusion-dependent patients at baseline was significantly higher in the non-IWGc group compared to the IWGc group (82% vs. 36%, respectively, $p<0.001$).

The pooled erythroid response rate from the meta-analysis based on a random-effects model using all epoetin alfa studies, including both non-IWGc and IWGc studies, was estimated at 43.9% (95% CI: 35.3–52.4%). The high I-squared value indicated the presence of heterogeneity across studies (I-squared: 85.1%) and the chi-square test for heterogeneity was statistically significant ($p<0.001$), justifying the choice of the random-effects model. As expected, the estimate of erythroid response rate was significantly higher for the IWGc studies (57.6%, 95% CI: 45.1–70.0%) as compared to the non-IWGc studies (31.6%, 95% CI: 24.9–38.4%; $p<0.001$), which demonstrate the importance of adjusting for IWGc in comparing erythroid response rates between epoetin alfa and darbepoetin alfa.

Table 2 Baseline characteristics of epoetin alfa patients, stratified by IWGc group

	Epoetin alfa IWGc (9 studies)	Epoetin alfa non-IWGc (13 studies)	*p* value
Enrolled patients	619	360	
Evaluable patients	589	336	
Mean age, years (SD)	71.0 (3.0)	71.4 (4.2)	0.792
Women, *n* (%)	290 (47.7)	128 (41.3)	0.065
RA/RARS, *n* (%)	424 (74.1)	230 (71.0)	0.309
Transfusion-dependent, *n* (%)	199 (36.1)	269 (82.3)	<0.001
Mean baseline Hb, g/dL (SD)	8.7 (0.7)	8.5 (0.5)	0.484
Mean baseline serum erythropoietin level, mU/mL (SD)	376 (98)	383 (421)	0.963
Initial weekly dose, units (SD)	47,851 (21,981)	47,249 (40,540)	0.966

IWGc International Working Group criteria, *SD* standard deviation, *RA* refractory anemia, *RARS* refractory anemia with ringed sideroblasts, *Hb* hemoglobin

Baseline disease characteristics and treatment regimens predictive of response in MDS

To identify study characteristics predictive of a higher erythroid respond rate in epoetin alfa IWGc studies, the univariate meta-regression analysis was performed. This analysis showed that a higher proportion of patients with refractory anemia or refractory anemia with ringed sideroblasts (RA/RARS; $p<0.001$), a lower mean baseline serum erythropoietin level ($p=0.007$), and receipt of a fixed dosing regimen compared to a weight-based regimen ($p<0.001$) were significant study characteristic predictors of higher response rates. Other factors that did not have a significant impact on erythroid response rate included baseline hemoglobin level ($p=0.375$). In studies where data were available, the weighted average time since diagnosis was significantly shorter for the IWGc studies as compared to the non-IWGc studies (Table 3).

Comparison of erythroid response rates between epoetin alfa and darbepoetin alfa

Nine epoetin alfa studies ($N=619$ patients; N evaluable=589) and eight darbepoetin alfa studies ($N=442$ patients; N evaluable=389) using IWGc to define erythroid response were identified for the analysis. Table 4 describes the baseline characteristics of patients treated with epoetin alfa vs. darbepoetin alfa. Baseline characteristics were similar between the two groups with respect to age, gender, proportion of patients with refractory anemia or refractory anemia with ringed sideroblasts, transfusion dependency rates, and mean baseline hemoglobin level. However, the mean baseline serum erythropoietin level was significantly higher in the epoetin alfa group than the darbepoetin alfa group (376 vs. 133 mU/mL, $p=0.003$). The average initial weekly dose in the epoetin alfa studies was 47,851 U (range 30,000–80,000 U), while that in the

Table 3 Relationship between MDS duration and overall erythroid response to epoetin alfa

Study	IWGc	Mean time since MDS diagnosis			sEPO level (mU/mL)	Transfusion-dependent (%)	Pooled erythroid response rate (%)
		N	Time (months)	Weighted average (months)			
Aloe Spiriti (2005)	Yes	133	11	12	335	49.5	60
Di Raimondo (1996)	Yes	12	8				
Stasi (1997)	Yes	43	16				
Marques da Costa (1994)	No	9	18	35[a]	323	87.4	28[b]
Ludwig (1993)	No	10	8				
Stenke (1993)	No	27	11[c]				
Stein (1991)	No	8	14				
Aloe Spiriti (1993)	No	23	19				
Rose (1995)	No	100	48				
Goy (1993)	No	17	50				

MDS Myelodysplastic syndromes, *IWGc* International Working Group criteria, *sEPO* baseline serum erythropoietin level

[a] Indicates that the weighted average time since MDS diagnosis was statistically significantly different between IWGc and non-IWGc studies ($p=0.0294$)

[b] Indicates that the erythroid response rate was statistically significantly different between IWGc and non-IWGc studies ($p<0.0001$)

[c] The information on time since MDS diagnosis was available only for responders (seven out of 27 patients)

Table 4 Baseline characteristics of epoetin alfa and darbepoetin alfa patients (IWGc studies)

	Epoetin alfa IWGc (9 studies)	Darbepoetin alfa IWGc (8 studies)	*p* value
Enrolled patients	619	442	
Evaluable patients[a]	589	389	
Mean age, years (SD)	71.0 (3.0)	73.7 (4.1)	0.174
Women, *n* (%)	290 (47.7)	205 (49.0)	0.672
RA/RARS, *n* (%)	424 (74.1)	293 (78.3)	0.139
Transfusion-dependent, *n* (%)	199 (36.1)	120 (39.2)	0.369
Mean baseline Hb, g/dL (SD)	8.7 (0.7)	9.2 (0.8)	0.260
Mean baseline serum erythropoietin level, mU/mL (SD)	376 (98)	133 (72)	0.003
Initial weekly dose, units/mcg (SD)	47,851 (21,981)	176 (59)	N/A

IWGc International Working Group criteria, *SD* standard deviation, *RA* refractory anemia, *RARS* refractory anemia with ringed sideroblasts, *Hb* hemoglobin

[a] The evaluable population included all patients enrolled in the studies that were eligible for the erythroid response assessment, per the clinical trial protocol.

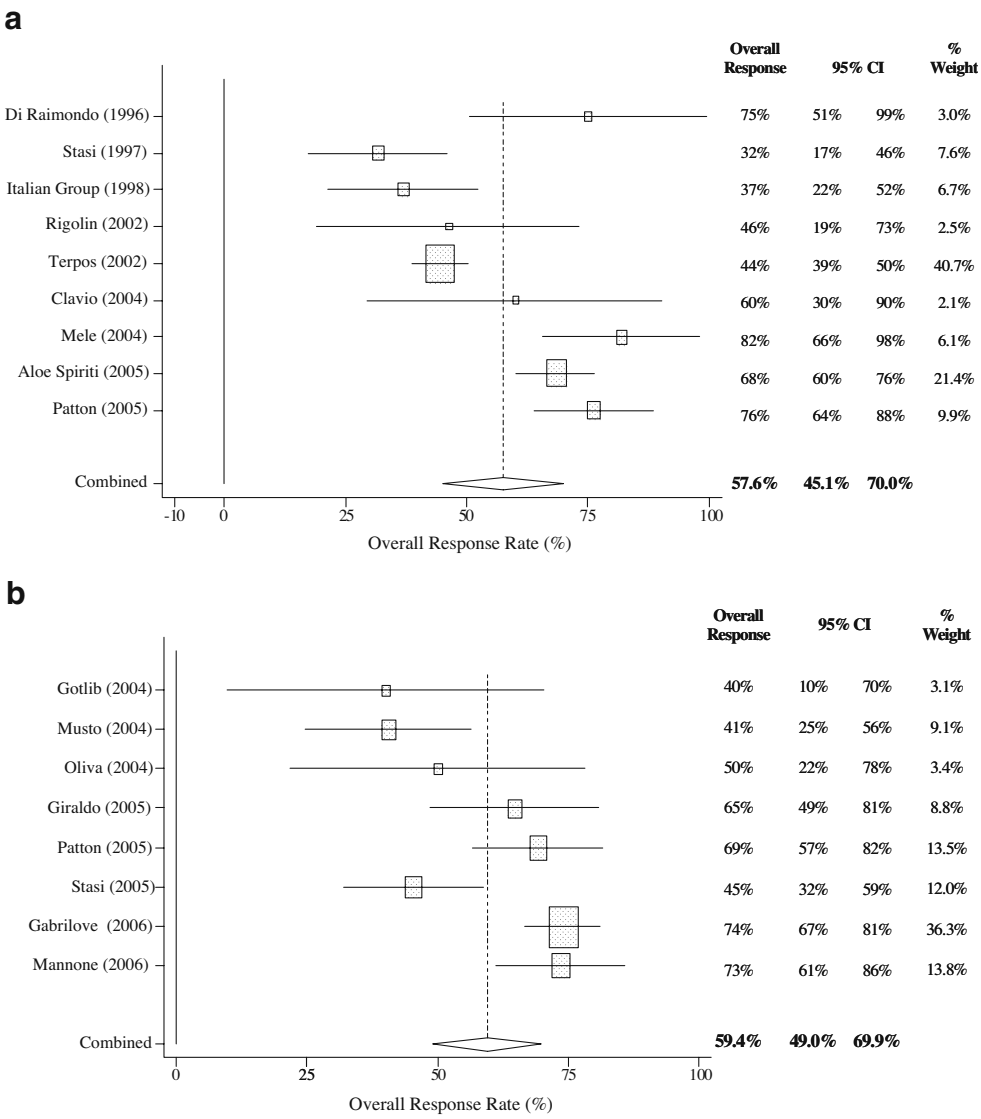


Fig. 2 **a** Overall erythroid response rates for epoetin alfa studies using IWGc. Notes: *Box symbol* denotes point estimate of response rate proportional to the study weight used to pool the results. *Line symbol* indicates the 95% confidence interval of response rate. **b** Overall erythroid response rates for darbepoetin alfa studies (all using IWGc). Notes: *Box symbol* denotes point estimate of response rate proportional to the study weight used to pool the results. *Line symbol* indicates the 95% confidence interval of response rate

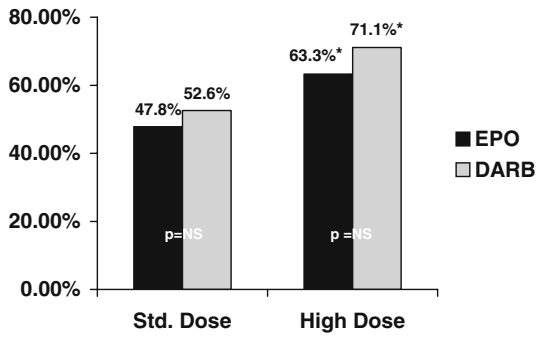
darbepoetin alfa studies was 176 mcg (range 100–315 mcg).

Figure 2a and b show that there was no significant difference in the pooled estimate of the erythroid response rates for either ESA (57.6%, 95% CI: 45.1–70.0% for the epoetin alfa studies vs. 59.4%, 95% CI: 49.0–69.9% for the darbepoetin alfa studies; $p=0.8282$). Furthermore, as shown in Fig. 3, when compared to the studies using standard weekly doses of epoetin alfa (30,000–40,000 U; five studies, 393 patients), those studies using higher dosing regimens (60,000–80,000 U; $n=4$ studies, 196 patients) showed a significantly higher erythroid response rate (47.8% vs. 63.3%, respectively, $p<0.001$). A similar dose relationship was also observed in the darbepoetin alfa group for studies using 100–150 mcg (four studies, 154 patients) vs. studies using 166–300 mcg (four studies, 235 patients; 52.6% vs. 71.1%, respectively, $p<0.001$, Fig. 3). No statistically significant difference was noted when erythroid response rates were compared between the two ESAs at corresponding dosing regimens.

Discussion

The present meta-analysis, using a comprehensive list of epoetin alfa and darbepoetin alfa studies, demonstrated higher erythroid response rates predominantly in the more recent studies that utilized IWGc to define response.

By contrast, the overall low erythroid response rate (31.6%) found in non-IWGc studies is similar to the modest efficacy of epoetin alfa observed in the first meta-analysis by Hellstrom-Lindberg in 1995 [16]. Comparatively little was known about MDS biology at the time of that publication. However, recently, greater refinement occurred in the treatment of these disorders. Noteworthy was the development of standardized response criteria, the IWG criteria, which permitted the comparison of efficacy of different agents in these rather diverse set of disorders. Additionally, the patient selection model proposed by Hellstrom-Lindberg et al. has defined the subset of patients that are most likely to benefit from ESA monotherapy or in combination with G-CSF and would thus be the best candidates for ESA therapy. According to the aforementioned model, endogenous serum erythropoietin levels ≤500 mU/mL and transfusion requirement of <2 packed red blood cell units per month are predictive of improved response to ESA [45]. The present meta-analysis supports these findings as evidenced by the percentage of transfusion-dependent patients being significantly higher in non-IWGc studies where, as mentioned above, response rates were lower as well. Therefore, although higher erythroid response rates in the IWGc group likely reflect inherent differences in the response definitions favoring the IWGc group, the improvement in response is perhaps a compound result of standardized criteria and more refined patient selection (i.e., inclusion of less severely ill patients in studies) over time. Further, the observation of higher response rates in studies incorporating a greater proportion of patients with RA/RARS is consistent with studies that found that epoetin alfa works best in lower risk patients [15, 17, 46]. Furthermore, our results provide further insights into the hypothesis that patients with disease of shorter duration are more likely to respond to epoetin alfa [17]. It is possible, however, that the effect of disease duration in our study might be sustained by other confounding factors, such as the observed proportion of transfusion-dependent patients at baseline. Therefore, the results from our meta-regression analysis should be interpreted cautiously because of lack of individual data.



Treatment	Standard Dose/ Week	High Dose/ Week
Epoetin Alfa	30,000 – 40,000 Units (n=5)	60,000 – 80,000 Units (n=4)
Darbepoetin Alfa	100–150 mcg (n=4)	166–300 mcg (n=4)

Fig. 3 Comparative erythroid response rates for epoetin alfa and darbepoetin alfa at standard doses and high doses. Note: *$p<0.001$ as compared to respective *Std. Dose*

Studies using darbepoetin alfa reported erythroid response rates similar to those seen with epoetin alfa when the two ESAs were compared on the basis of IWGc. Moreover, both ESAs seem to yield higher but comparable erythroid response rates with the use of higher weekly doses (60,000–80,000 U for epoetin alfa and 166–300 mcg for darbepoetin alfa). When epoetin alfa and darbepoetin alfa studies were compared based on utilization of IWGc, relatively lower endogenous erythropoietin levels (376 vs. 133 mU/mL, $p=0.003$) were found on studies involving darbepoetin alfa. Interestingly however, the erythroid response rates were comparable to those in the epoetin alfa studies, supporting the cut-off point of 500 mU/mL of endogenous erythropoietin used by the predictive model described above.

Higher dosing regimens of both epoetin alfa (weekly dose 60–80 K U) and darbepoetin alfa (weekly dose 166–300 mcg) were associated with improved erythroid

responses. The optimal dose of either ESA for MDS remains to be determined and perhaps a prospective randomized dose finding study is warranted for both agents.

This study similar to meta-analyses in general has limitations. First, only epoetin alfa studies were considered for the present analysis. Studies using epoetin beta, an ESA not available in the United States, were not included because of the very small number of available reports with this agent. Secondly, studies, although few, were included from peer-reviewed abstracts/posters. A differential distribution of such reports in different study groups may introduce an information bias. In the present analysis, 4/8 darbepoetin alfa studies were in the abstract/poster form as compared to 1/9 IWG epoetin alfa studies. Thirdly, although meta-analysis has the ability to improve the power of small or inconclusive studies, it cannot improve the quality or reporting of the original studies. Fourthly, the lack of primary source data from the original studies is also a further limitation to the analysis, as ecological bias may influence results [47]. In this analysis, the original studies were weighted based on the method of DerSimonian and Laird [22], which tends to favor studies with a larger sample size. However, the quality of the original studies (e.g., randomized vs. observational design) was not considered. Lastly, the total number of epoetin alfa and darbepoetin alfa studies in MDS is relatively small and data regarding reported durations of follow-up are limited, suggesting that these results be considered as hypothesis generating. Further head-to-head randomized trials are necessary to compare the validity of the present results regarding efficacy of epoetin alfa and darbepoetin alfa in MDS.

Safety endpoints were not assessed in this meta-analysis. When ESAs are used according to product labeling in the setting of chemotherapy-induced anemia (target hemoglobin not to exceed 12 g/dL), no effect on survival or other tumor outcomes has been observed [48, 49]. Recent safety signals that have emerged in cancer studies have all been related to investigational uses (treatment beyond correction of anemia, "anemia of cancer", and potentiation of head and neck cancer radiotherapy). Interestingly, there are recent retrospective reports suggesting that for MDS, the use of ESAs as monotherapy or in combination with G-CSF, is associated with improved survival [50–53]. This is plausible considering the possible impact of transfusion and related iron overload on survival in MDS patients [6, 54, 55]. Furthermore, transfusion-dependent patients are likely to have lower Hb values than non-transfusion-dependent patients, and anemia has been shown to be a significant risk factor for both survival and cardiovascular diseases [4, 56]. It is not unreasonable to speculate that ESAs, by reducing transfusion dependency and correcting anemia, may positively impact survival. However, the counterargument is that transfusion dependence in itself is likely to be an indicator of more severe disease and, as such, it is unlikely that ESAs would reduce the risk of leukemic evolution [54]. On the other hand, it is worthwhile to note that in lower risk MDS, causes of death are not only related to leukemia but also include predominant nonleukemic causes such as cardiac complications (50%), infectious diseases (30%), bleeding (8%), and liver failure (8%) [6]. The causes of death, with the exception of thrombocytopenia-related bleeding, are similar to those found in other disease states such as the thalassemias where chronic transfusion results in iron overload [57, 58]. However, the true risk benefit assessment of ESAs in MDS can only be evaluated in prospective well-designed randomized placebo-controlled studies.

Conclusion

This meta-analysis of patients with MDS treated with epoetin alfa showed significantly higher erythroid response rates over time, particularly in studies utilizing IWGc to define response. The main reason for this finding is improved patient selection and standardized response criteria over time. The current analysis also demonstrated that, in studies using standardized patient selection and response evaluation methods, epoetin alfa and darbepoetin alfa yielded comparable erythroid response rates in anemic MDS patients. Prospective randomized clinical studies are required to evaluate the long-term benefit and safety of ESAs in MDS.

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