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Assessment of the reporting quality of RCTs for erythropoiesis-stimulating proteins in myelodysplastic syndrome from 1998 to 2018

Αξιολόγηση της ποιότητας αναφοράς των τυχαιοποιημένων κλινικών μελετών για του παράγοντες διέγερσης της ερυθροποίησης στα μυελοδυσπλαστικά σύνδρομα από το 1998 έως το 2018

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Περίληψη

Εισαγωγή. Οι παράγοντες που διεγείρουν την ερυθροποίηση (ESP) έχουν χρησιμοποιηθεί για τη θεραπεία της αναιμίας σε ασθενείς με μυελοδυσπλαστικό σύνδρομο (MDS) για πολλά χρόνια. Η παρούσα μετα-ανάλυση διεξήχθη για να εκτιμηθεί η αποτελεσματικότητα και η ασφάλεια δύο ESP πρωτεϊνών, της εποετίνης και της darbepoetin στην αναιμία του MDS.

Μέθοδοι. Μια συστηματική ανασκόπηση και μετα-ανάλυση διεξήχθη, που συμπεριλάμβανε μελέτες στην αγγλική γλώσσα, από το 1998 έως το 2018, στις οποίες οι ασθενείς έλαβαν θεραπεία με ESP. Οι συγκεντρωτικές εκτιμήσεις των ποσοστών της απόκρισης ερυθροποίησης υπολογίστηκαν σε κάθε ομάδα χρησιμοποιώντας μεθόδους μετα-ανάλυσης σταθερών επιδράσεων. Η πολυπαραγοντική ανάλυση μετα-παλινδρόμησης διεξήχθη περαιτέρω για τον έλεγχο διαφορετικών χαρακτηριστικών μεταξύ των δύο ομάδων.

Αποτελέσματα. Πέντε RCTs συμπεριλήφθησαν: τέσσερεις για την εποετίνη και μία για τη δαρβεποετίνη. Οι ασθενείς με ESP έδειξαν σημαντικό πλεονέκτημα έναντι των μαρτύρων όσον αφορά τις αποκρίσεις αιμοσφαιρίνης (Hb) (OR: 5.59, διάστημα εμπιστοσύνης 95%, 2.74-11,42). Η απόκριση της Hb ήταν 24% στην ομάδα ESP και 5.6% στους μάρτυρες. Κανένας από τους παράγοντες που επηρεάζουν την απόκριση της Hb (ηλικία, φύλο, αριθμός συμμετεχόντων, τύπος ESP και διάρκεια ESP) δεν ήταν σημαντικός. Τα ποσοστά των ανεπιθύμητων ενεργειών δεν διέφεραν μεταξύ των ομάδων.

Σκοπός. Ο σκοπός ήταν να εκτιμηθεί αν αυξάνεται η ερυθροποίηση σε ασθενείς με MDS που υποβλήθηκαν σε θεραπεία με ESPs με μια συστηματική ανασκόπηση της βιβλιογραφίας.

Συμπεράσματα. Δημοσιευμένες μελέτες υποδεικνύουν ότι οι ESP είναι αποτελεσματικές στην αναιμία του MDS. Η ανταπόκριση της Hb εμφανίζεται υψηλότερη στους ασθενείς που έλαβαν ESP και δεν αναφέρθηκαν σημαντικές ανεπιθύμητες ενέργειες. Αλλά τα δεδομένα για την δαρβεποετίνη είναι λίγα και δεν υπάρχουν ακόμη πολλές RCTs.

Λέξεις-κλειδιά. Αναιμία • MDS • Μετα-ανάλυση • Εποετίνη • Δαρβεποετίνη

Abstract

Introduction. Erythropoiesis-stimulating proteins (ESPs) have been used in the treatment of anemia in MDS patients for many years. The present meta-analysis was conducted to assess the efficacy and safety of two ESPs, epoetin and darbepoetin in anemia of myelodysplastic syndrome (MDS).

Methods. A systematic review, and meta-analysis was conducted covering English-language studies, from 1998 to 2018, in which patients treated with ESPs was performed. Pooled estimates of ER rates were calculated in each group using fixed-effects meta-analysis methods. Multivariate meta-regression analysis was further conducted to control for different characteristics between the two groups.

Results. Five RCTs qualified: 4 four epoetin versus controls and one darbepoetin versus controls. ESPs patients demonstrated a significant advantage over controls in terms of hemoglobin (Hb) responses (odds ratio: 5.59, 95% confidence interval, 2.74–11.42). Hb response was 24% in ESPs group and 5.6% in controls. .None of the analyzable predictors of Hb response (age, gender, number of patients, ESP type, and ESP duration) was significant in meta-regression analyses. Selected adverse event rates did not differ between the groups.

Purpose. The purpose was to assess erythroid response rates in MDS patients treated with ESPs by performing a systematic review of the literature.

Conclusions. Published studies suggest that ESPs are efficacious in anemia of MDS. Hb response appears higher in ESPs patients and no significant adverse events reported. But darbepoetin data are sparse, and there are not as yet many RCTs.

Key Words. Anemia • MDS • Meta-analysis • Epoetin • Darbepoetin

Introduction

Myelodysplastic syndromes (MDS) are a heterogenous group of hematopoietic stem cell disorders categorized under chronic myeloid malignancies according to the World Health organization (WHO) 2016 classification.[1] It is 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)[2]. The incidence rate of these conditions is about 5 cases per 100.000 persons per year in the general population, but increases to 20 to 50 cases per 100.000 persons per year after age 60 years. This means that approximately 25.000 new cases are expected in Europe each year. Moreover, considering the progressive aging of the population in Europe, the number of MDS patients is destined to increase in the next decades.[3] Moreover, in the U.S. although the rates are lower, the American Cancer Society estimates 7.000–12.000 new cases per year.[4] Although MDS is increasingly well understood from a biological standpoint, including discovery of 40 MDS-associated recurrently mutated, improved pathological in sight has not yet translated into highly effective or curative therapies for most patients suffering from these disorders.[5]

The revised Classification 2016 WHO guidelines identify 6 entities of MDS: MDS with single lineage dysplasia (MDS-SLD); MDS with ring sideroblasts (MDS-RS); MDS with multi lineage dysplasia; MDS with excess blasts (MDSEB); MDS with isolated del (5q); and MDS unclassifiable (MDS-U) (Table 1). The current introduces refinements in morphologic interpretation and cytopenia assessment and addresses the influence of rapidly accumulating genetic information in MDS diagnosis and classification. Cytopenia is a “sine qua non” for any MDS diagnosis and in prior classifications, MDS nomenclature included references to “cytopenia” or to specific types of cytopenia (eg, “refractory anemia”). However, the WHO classification relies mainly on the degree of dysplasia and blast percentages for disease classification and specific cytopenias have only minor impact on MDS classification. Moreover, the lineage(s) manifesting significant morphologic dysplasia frequently do not correlate with the specific cytopenia(s) in individual MDS cases. For these reasons, the terminology for adult MDS has changed to remove terms such as “refractory anemia” and “refractory cytopenia” and replaces them with “myelodysplastic syndrome” followed by the appropriate modifiers: single vs multilineage dysplasia, ring sideroblasts, excess blasts, or the del (5q) cytogenetic abnormality. There are no changes to childhood MDS; refractory cytopenia of childhood remains as a provisional entity within this category (Table 1).[1,6]

A large amount of data has recently become available on recurring mutations in MDS. Targeted sequencing of a limited number of genes can detect mutations in 80% to 90% of MDS patients; the most commonly mutated genes in MDS are SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53, and EZH2.[7] Importantly, acquired clonal mutations identical to those seen in MDS can occur in the hematopoietic cells of apparently healthy older individuals without MDS, so-called “clonal hematopoiesis of indeterminate potential” (CHIP).[2] Although some patients with CHIP subsequently develop MDS, the natural history of this condition is not yet fully understood; thus, the presence of MDS-associated somatic mutations alone is not considered diagnostic of MDS in this classification, even in a patient with unexplained cytopenia, where these mutations may be commonly found.[8]

Table 1. Classification of MDS (2016)

Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood
Myeloid neoplasms with germ line predisposition

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.[9] Specific MDS treatment strategies are also based on the risk stratification by the International Prognostic Scoring System (IPSS) are recommended in the National Comprehensive Cancer Network (NCCN) Guidelines.[10] Treatment choices for MDS are varied and include cyclosporine, thalidomide and its derivatives, tumor necrosis factor inhibitors, cytarabine, and 5-azacytidine.Treatment to improve cytopenia is recommended for patients with IPSS low or intermediate-1 risk. Most patients in the lower risk categories die from causes other than leukemia.[11] In these patients, the course of disease is marked by prolonged survival with chronic cytopenias and infrequent evolution to AML. For patients with intermediate-2 or high risk, the guidelines recommend radical treatment with a hematopoietic stem cell transplant or treatment to decrease the blast count to delay the progression to AML. Bone marrow transplantation is the best hope for cure, but this procedure is limited by donor availability and significant toxicity, especially in the older population, which MDS commonly afflicts. While the ultimate goal of treatment is to extend survival, treatment is also intended to prevent the leukemic progression that occurs in up to 30% of patients. 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 (QoL), while minimizing side effects of therapy.[9]

MDS occurs primarily in the elderly population, with a median age between 60 and 75 years. Fatigue and exertional dyspnea may develop over a prolonged period, often exceeding 6–12 months. These symptoms may be misinterpreted as either cardiac failure or pulmonary disease, particularly in elderly patients. Approximately half of the individuals are asymptomatic at the time of initial diagnosis and are usually diagnosed after a routine blood count. Progressive hematopoietic failure leading to anemia, thrombocytopenia, and leukopenia, either alone or in

any combination is the dominant finding in MDS. Anemia is an almost universal characteristic at the time of initial diagnosis; more than 80% of patients present with a hemoglobin concentration below 10 g/dl. The reticulocyte count usually is reduced.[12] Anemia is a major contributor to the symptomatology of MDS, because it is associated with fatigue, weakness, and shortness of breath. These effects of anemia may be temporarily ameliorated by RBC transfusions. 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. Furthermore, transfusion therapy places great strain on the limited donor blood supply, which faces daily challenges of collection, processing, and distribution.[13]

Erythropoiesis stimulating proteins (ESPs) administered either alone or in combination with granulocyte or granulocyte–macrophage colony-stimulating factors (G-CSF or GM-CSF), have been tested and used in anemic MDS patients. Also, has been extensively studied as a means to improve erythropoiesis and reduce red blood cell transfusions in MDS patients with anemia.[14]The ability of patients with diseased bone marrow to respond to ESPs has been questioned, and concerns regarding safety, especially the potentiation of leukemic progression by an exogenous growth factor, have been raised as possible objections to using ESPs in MDS. That's because the use of ESPs was 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] Recently, darbepoetin alfa, has also been shown to be effective in the treatment of MDS-related anemia.[16] Moreover, the last years random clinical trials of ESPs, have been conducted.[17,18,19,20,21] Two meta-analyses reported a significantly higher erythroid response with ESPs, compared to a controlled drug (odds ratio, 5.2; 95% confidence interval, 2.5–10.8) and also was no significant difference in the pooled erythroid response rates between the two agents (epoetin alfa: 57.6% vs. darbepoetin alfa: 59.4%; $p = 0.828$). [22,23] Patients with MDS are known to have higher serum erythropoietin (EPO) levels than healthy adults. Higher serum EPO levels are inversely associated with a patient's response to ESPs. Based on these study reports, the NCCN Guidelines recommend ESAs as a first-line treatment for MDS patients with IPSS low or intermediate-1 risk, symptomatic anemia, and a serum EPO level of ≤500 mIU/mL.[24] 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. 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.[25]

The purpose of the present meta-analysis was: to assess erythroid response rates in MDS patients treated with ESPs (epoetin and darbepoetin), to gain further insights into predictors of

response rates, and to compare the erythroid response rates observed with epoetin alfa and darbepoetin.

Methods

In general, the methods used for this review followed current best practices for conducting systematic reviews and meta-analyses of the literature.[26]

Studies

The literature search was electronically. MEDLINE (via PubMed) was searched using the following search strategy:

1.EPO OR epoetin OR erythropoietin OR erythropoiesis-stimulating proteins OR darbepoetin

2. Myelodysplastic syndromes OR MDS OR myelodysplasia.

3. #1 AND #2.

Also the electronic databases Scopus and Cochrane were searched for relevant citations.

In the selection of studies were limits: Publication date 1998–2018, RCTs, English, and human, NOT single-arm studies, case reports, letters, news, editorials, reviews, preclinical studies, retrospective analyses.

There were no restrictions on sample size and duration of study. If the relevant data for the analysis were available from the abstract, it was acceptable. All RCTs and abstracts that evaluated the effectiveness of epoetin or darbepoetin as a monotherapy for the treatment of MDS-related anemia were included. Studies had to report at least one of the following outcomes of interest: hemoglobin (Hb) change, RBC transfusions, number of patients with Hb response. Selected adverse events (AEs) were also sought: deaths, patients progressing to acute myelogenous leukemia (AML), asthenia and fatigue.

Randomized controlled trials (RCTs) were also critically appraised at the time of data extraction using the CONSORT 2010 checklist (CONsolidated Standards Of Reporting Trials). Each accepted RCT was scored for features of randomization method used, blinding of treatments, and accounting for all patients entered and withdrawn.

Data extraction

For each eligible study, we extracted information on authors, year of publication, countries of recruitment, diagnostic criteria, gender, types of ESP, number of patient, concurrent treatment and dosing duration.

Statistical Analyses

Study-, patient-, and treatment-level data were summarized using basic descriptive statistics (simple counts and means). The number of patients randomized or enrolled was used in

the calculation of study and patient demographics. The main objective of the analyses was to quantify and compare the efficacy for managing anemia in MDS patients. Outcomes of interest included: Hb response, as well as major and minor response and transfusions. [27] 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. Frequency counts and percentages were used to summarize categorical variables while means and standard deviations were used for continuous variable.

Fixed-effect model meta-analyses were used to calculate pooled ORs with 95% CI for Hb response. The FE does not consider the variability across studies and assumes that the studies are homogeneous in terms of θi. Thus, in order to use the FE model, we first tested whether a significant heterogeneity across studies exists. Because heterogeneity does not exist, then is eligible to use the FE model; otherwise the random model should be used. The RE model is a more conservative methodology for combining results across studies, taking into consideration both within-and between-study variation. The test for heterogeneity is based on the formula Q-statistic which is a weighted sum of squares of the deviations of individual trial treatment difference θi from the pooled estimate θp. If Q is less than the 10% point of the χ2-distribution with n-1 df (given from the table of the χ^2-distribution), there is no significant heterogeneity across studies.[28] In addition, univariate meta-regression analyses were conducted, with supplemental descriptive statistics, to identify study characteristics that were significant determinants of erythroid response rate using epoetin alfa IWGc studies.

The results from the studies which were meta-analyzed, are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) for active versus control treatments. An OR <1 indicates a lower risk for active than for control treatment, and an OR >1 indicates a greater risk for active than for control treatment.[29]

Meta-regressions were conducted to test the impact of some covariates upon the main efficacy outcome. The covariates of interest had comprehensive and well-distributed results available across trials. These were: number of patients, gender, ESP type (epoetin or darbepoetin) and ESP duration (weeks). None of the covariates were significant. Other covariates were of interest, but insufficiently reported to use in the meta-regression analyses of predictors.

In the extraction of safety data, a zero was extracted only when there was a statement to the effect that a particular event did not occur. No assumptions were made from the absence of data and did not included in analyses. Moreover, it was taken in account if there is publication bias. The simplest and most commonly used method to detect publication bias is an informal examination of a funnel plot. Also, a formal test for publication bias based on linear regression analysis is Egger's test. If t from Egger's test is less than the 5% point of the t-distribution with n-1 df, there is no indication of publication bias. All calculations were performed using SPSS software version 24 (SPSS, Inc., Chicago, IL) and Revman 5.3

Results

Five RCTs (n= 459) were eligible for inclusion in this meta-analysis. There were published in 1998–2018. The four of five RCTs studied response to epoetin a and one to darbepoetin. The darbepoetin study was the most recent (2017). One study was available only as abstract (Miller et all). Three studies were in counties of Europe and two were in America. . The men outnumbered women (60% versus 40%), and the average age was 71 years (Table 2). Study durations (available in all studies) were in the range of 12–52 weeks (averaging 22.5 weeks) and dose frequency variable among the studies. There were no darbepoetin versus epoetin studies. Extractable Hb response outcomes were available in all RCTs. The distribution of groups and patients by ESP type, dosing duration frequency, and duration is shown in Table 3.

ESP efficacy and safety outcomes were rarely reported by baseline risk category. Two RCTs studied the response in the 3 groups of anemia: patients with refractory anemia RA with ringed sideroblasts, and RA with excess blasts (RAEB). Concomitant G-CSF or GM-CSF was used in two RCTs. Further delineation of major and minor Hb response was available in only two studies and transfusion outcomes also in two studies. Most authors reported dose reduction rules in the event of exceeding the target Hb or in the event of toxicity. Furthermore, all studies reported adverse events (AEs). Concurrent iron (as an oral supplement) was identified in only one study. The remaining studies were silent on the use of iron. In only one was the baseline serum erythropoietin level (<500 U/l) reported (Hb response OR:29.5, CI:1.9–531.2).

Table 2. Patient's characteristics

Author	Year	Ethnicity	Number of patient	Mean age, years	Men, %
Platzbecker	2017	Europe	147	74	54.8
Miller	2004	USA	109	73	NA
Pierluigi	1998	Europe (Italy)	77	65	65
Casadevall	2004	Europe (French)	60	72	50
Thompson	2000	USA	66	62.5	70

Table 3. Anemia treatment characteristics: ESP treatment groups

Author	ESP type	Dosing frequency	Dosing duration
Platzbecker	Darbepoetin a	Once per 3 weeks	24 weeks
Miller	Epoetin a	Every day	16 weeks
Pierluigi	Epoetin a	Every day	8 weeks
Casadevall	Epoetin a	3 times a week	12 weeks
Thompson	Epoetin a	3 times a week	12 weeks

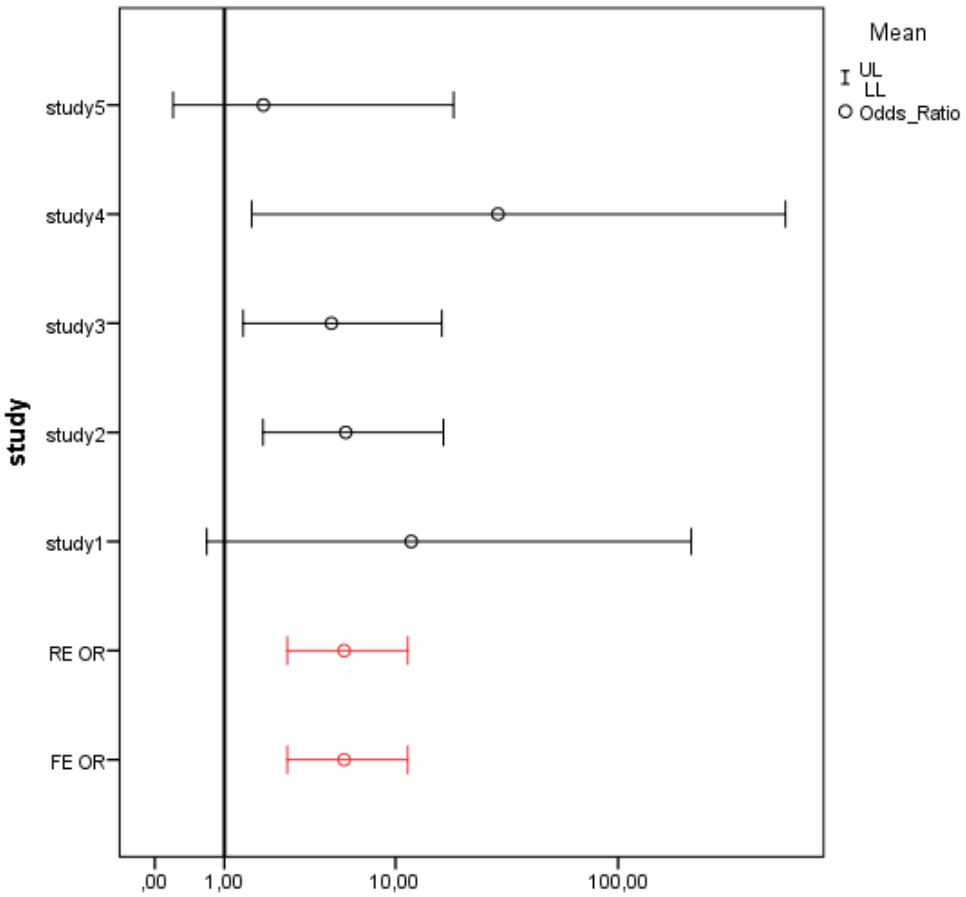
Efficacy of ESPs in MDS

The main outcome of interest was the percentage of patients with Hb response. All studies used similar, but not exactly identical, criteria for Hb response. The main criteria were increase in Hb and need for transfusion. The most studies used the IWG criteria (or minor modifications).[30] Definitions of response criteria were defined as follows: full response: increase in Hb)>2g/dl (two consecutive controls in the same week) or no transfusion for at least 2 months; partial response: increase in Hb of 1–2g/dl (two consecutive controls in the same week) or 50% decrease in transfusion need for at least 2 months; no response: Hb change <1 g/dl or <50% reduction of transfusion requirements. Hb overall response is the sum of the major and minor responders. All five studies was this outcome available and analyzable. The Hb response rate was 24% ESPs group, and in control groups it was 5.6% (Table 4). The OR for Hb response was 5.59 (CI:2.74-11.42), significantly in favor of ESPs. An OR=5.59 means that there is 5.5 times greater chance of response when treated with ESPs than with placebo. There was no significant heterogeneity among the RCTs (P-value for Q=0.678). Heterogeneity was considered present when the P value of the Cochran Q test was P> 0.10, and so only the FE OR was considered. Note that RE OR coincides with the FE OR. The advantage for ESP was evident across all RCTs and reached statistical significance in three of five the studies (Fig. 1).

Table 4. ESPs vs control: Hb response

	Treatment		Control		OR	CI
	success	total	success	total		
Platzbecker	11	75	0	35	11.86	0.68 – 207.96
Miller	19	53	5	56	5.70	1.94 – 16.73
Pierluigi	14	38	4	37	4.81	1.41 – 16.45
Casadevall	10	30	0	30	29.50	1.63 – 532.26
Thompson	4	45	1	21	1.95	0.20 - 18.62

Figure 1. Odds Ratio and 95%Cl



In two studies the dosing frequency was three times per week, in two it was every day and in the remaining study was once per 3 weeks. The dosing duration was 12 weeks in two RCTs, 8 weeks in one, 16 weeks in the other and 24 in the last one. Studies with a longer duration (16 and 24 weeks) of ESPs use about the same Hb response rate (23.4%) (OR:6.24, Cl:2.,28-17.10) with studies with a shorter duration (8 and 12 weeks) of epoetin use (24.7%) (OR:5.01, Cl:1.82-13.77) (p=741).The duration of response and relapse rates were not efficacy outcomes for this analysis, and were rarely reported, because most studies did not provide long-term follow-up information. Casadevall et al reported that six of eight patients who continued epoetin past the initial 12-week study period relapsed, but they did not report time to relapse. Studies which the populations are from Europe (OR:6.91, Cl:2.41-19,78) had similar outcomes with studies from USA (OR:4.6, Cl:1.77-12.34)

In one RCT there was analyzable data for major and minor response. The average major response rate in ESPs group was 13.2% (OR:5.3, Cl:0.59-47.2) and the minor response rate was 23.7% (OR:2.56, Cl: 0.71-9.20) (Table 5). (Note: The major and minor response rates do not equal the total response rate here because of different studies contributing to each estimate.) In the four of five RCTs it was used epoetin a and in the remaining darbepoetin a. In the epoetin group the total Hb response rate was 26.5% (OR:5.32, Cl:2.55-11.12). The OR is significant at P<0.05 and there is 5 times greater chance of response to ESP than to placebo. While in the darbepoetin study response rate was 14.7% (11/75 evaluable) versus 0% (0/35 evaluable), (P=0.016) (OR: 5.85, CI: 0.72-47.2). Efficacy outcomes for the epoetin a studies and darbepoetin study are displayed in

Table 6. Figure 2 summarizes the meta-analyzed results for Hb response outcomes for each type of treatment and type of response (minor and major). It appears that darbepoetin has inferior results, but the 95%CIs overlap with those of epoetin. Furthermore, the rate of transfused patients is 49.3% in ESPs group and 68.6% in control group. The OR=0.45 means that there is 55% less chance of transfusion when patients treated with ESPs than with supportive treatment.

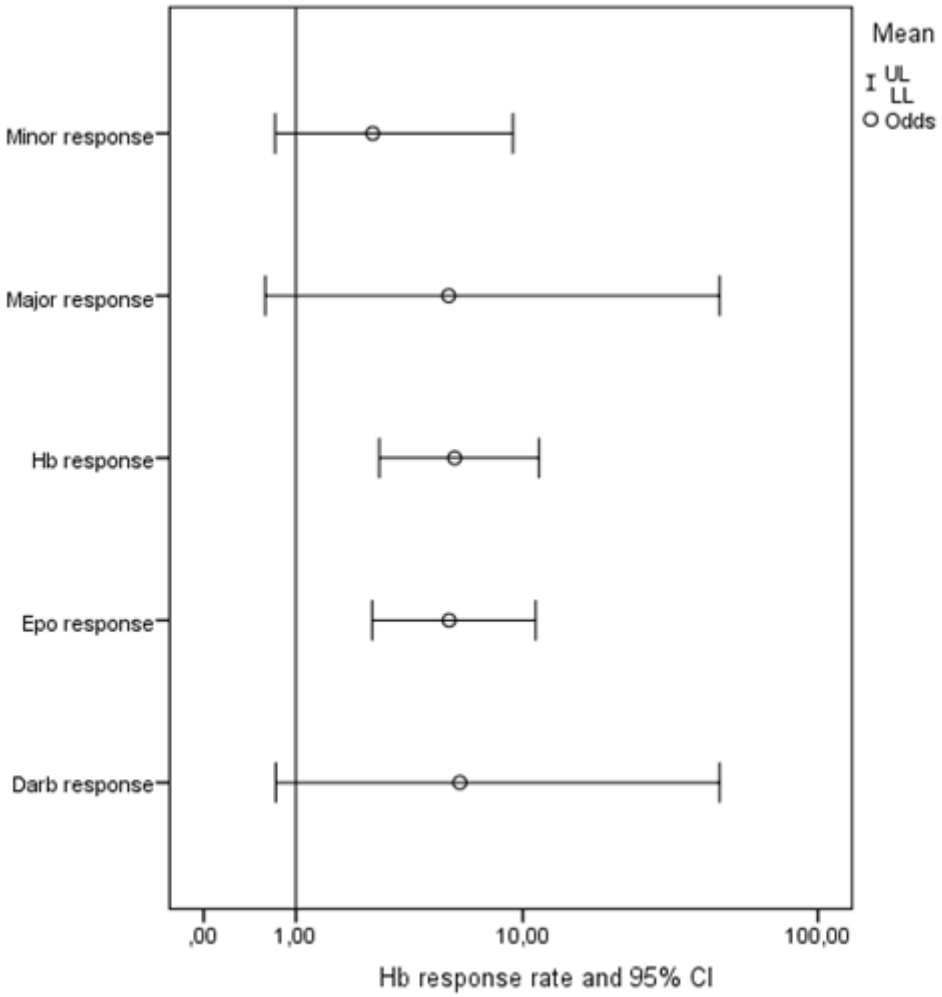
Table 5. Anemia response in MDS RTCs

	n of studies with available data	ESPs		Control		Odds ratio (95% CI)
		(n)	%	(n)	%	
Hb responders (%)	5	241	24	179	5.6	5.59 (2.74-11.42)
Major	1	38	13.2	37	0.0	5.3 (0.59-47.2)
Minor	1	38	23.7	37	10.8	2.56 (0.71-9.20)
Patients transfused (%)	2	142	49.3	70	68.6	0.45 (0.24- 0.81)

Table 6. Epo vs Darb - anemia response

Type of ESPs	n of studies with available data	ESPs		Control		Odds ratio (95% CI)
		(n)	%	(n)	%	
Epoetin a	4	166	26.5	144	7	5.32 (2.55-11.12)
Darbepoetin	1	75	14.7	35	0.0	5.85 (0.72-47.2)

Figure 2. Odds Ratio and 95% CI for time of treatment and type of response



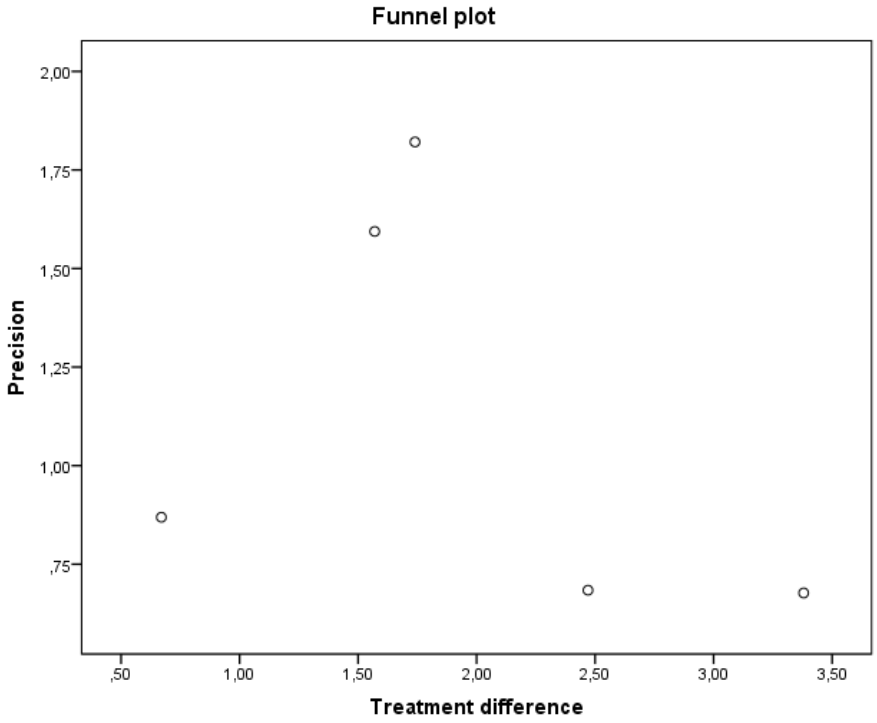
No concomitant chemotherapy, immunotherapy, hematopoietic stem cell transplant, other epigenetic therapy, or investigational treatments were included in the studies. Three used concurrent G-CSF or GM-CSF (Hb response OR:5.3, 95%CI:2.1-13.44), and one used concurrent oral iron (Hb response OR:4.6, 95% CI:1.4–15.2). The use of concomitant G-CSF showed little difference in efficacy outcomes (25% Hb response) compared with overall results (24% Hb response) (P=0.869) and with the studies which didn't use concurrent treatment (OR:5.54, CI:1.79-17.14) (P=0.617) (Table 7). In only one was the baseline serum erythropoietin level <500 U/l) reported (Hb response OR:29.5, 95% CI:1.9–531.2).

Table 7. ESPs vs control efficiency with concurrent treatment

Concurrent treatment	n of studies with available data	ESPs		Control		Odds ratio (95% CI)
		(n)	%	(n)	%	
G-CSF or GM-CSF	3	128	25	107	5.6	5.3 (2.1-13.44)
None	2	113	22	72	4.6	5.54 (1.79-17.14)

Although, there was not heterogeneity in the analysis a meta-regression was conducted in order some baseline covariates upon the main efficacy outcome. The covariate age does not affects the response, P-value for b = 0.182 (P>0.10, not significant). Moreover, meta-regression analysis for the covariates: number of patients (P-value 0.842), ESPs type (P-value 0.657), gender (P-value 0.778) and duration (P-value 0.842) was not significant. Also, a sensitivity analysis for publication bias was conducted. The Egger's test was used the regression analysis. The P-value for testing whether the intercept a is 0 is P=0.528, i.e. the intercept a is not significant since P≥0.05. Therefore, there is no significant publication bias in the meta-analysis. Moreover, in the funnel plot there isn't asymmetry that indicates the absence of publication bias (Fig 3).

Fingure 3. Funnel plot for publication bias



Safety of ESPs in MDS

In none RTCs were reported statistical significant adverse events. But only in two RCTs the data were reported analytically (Platzbecker and Thomson). In order to Platzbecker et al the most frequently adverse events were patient-reported fatigue (darbepoetin alfa: 17.3%, placebo: 8.3%), asthenia (darbepoetin alfa: 12.2%, placebo: 10.4%) and exertional dyspnea (darbepoetin alfa: 6.1%, placebo: 10.4%). In order to Thomson et al the most frequently adverse events were skin reaction at rejection site (epoetin a: 33%, placebo: 57%), hepatomegaly (epoetin a: 8%, placebo: 16%), splenomegaly(epoetin a: 8%, placebo: 16%), erythema (epoetin a: 6%, placebo: 19%), myalgia (epoetin a: 6.7%, placebo: 14.3%), thrombocytopenia (epoetin a: 11.1%, placebo: 0%), chills(epoetin a: 2%, placebo: 4%), headache (epoetin a: 2%, placebo: 4%), asthenia/fatigue

(epoetin a: 4%, placebo: 0%), pain in extremities (epoetin a: 2%, placebo: 0%), pyrexia (epoetin a: 2%, placebo: 0%), allergic (epoetin a: 2%, placebo: 0%), stroke (epoetin a: 2%, placebo: 0%) and pericarditis (epoetin a: 2%, placebo: 0%). In Casadevall et al study, there were no adverse effects attributable to rHuEPO or rHuG-CSF and none of the deaths were linked to the treatment evaluated in the study. Although, one patient from ESPs group progressed to AML after 10 weeks of treatment, and another from control did so 20 weeks after inclusion. Moreover, in Pierluigi et al study adverse events occurred in 31.8% of the rHuEpo-treated versus 42.9% of the placebo-treated patients (P=0.29, not statistical significant), but discontinuation of treatment before the eighth week was necessary only in seven cases (disease progression, one/each group; inefficacy of treatment, one/each group; stroke, one (epoetin a); skin rash, one; and personal reason one (both in the placebo group). The last study (Miller et al), the treatment was not associated with an increase rate of transformation to acute leukemia. Toxicities were comparable in all the treatment groups.

Safety of ESPs in MDS

Table 8. Adverse events of ESPs in MDS

Category	ESPs			control			Odds ratio (95% CI)
	n total	n AEs	%	n total	n AEs	%	
Total AEs	166	14	11.9	125	20	16	0.53 (0.24-1.19)
Serious AEs	143	20	14	69	12	17.4	0.76 (0.35-1.68)
Fatal AEs	143	4	2.8	69	3	14.3	0.60 (0.11-3.24)
Thrombocytopenia	45	5	11.1	21	0	0	5.13 (0.08-44.21)
Asthenia/fatigue	143	27	18.9	69	9	13	1.51 (0.66-3.45)
Progression to AML	128	3	2.3	78	2	2.6	0.99 (0.16-6.21)

Figure 4. Odds ratio and 95%Cl for AEs

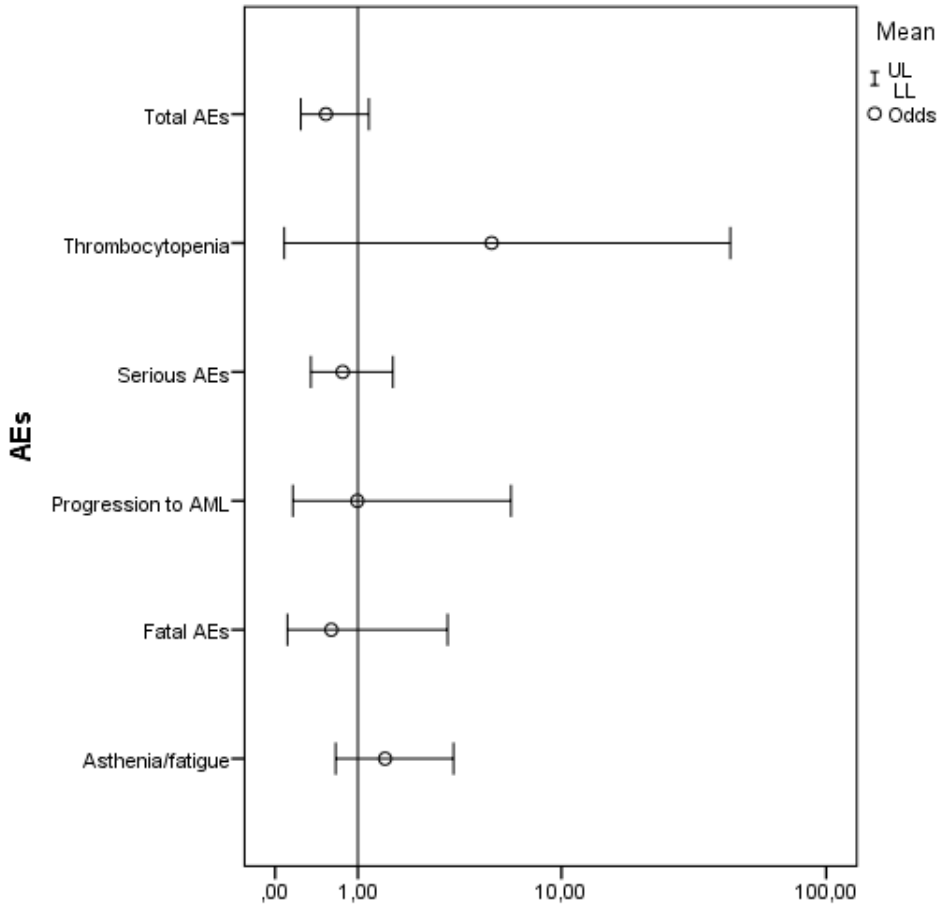


Table 8 shows the frequencies of total and selected AEs, as well as the OR for these AEs. In these studies, event rates for all AEs captured were relative low. There wasn't significant difference in the AEs rates (OR:0.53, Cl:0.24-1.19). None of the ORs in the selected AEs reached statistical significance. Odds ratio reported only for same study groups reporting event. The rates of serious and fatal AEs were higher in placebo group (not significant, OR:0.76, Cl:0.35-1.68 and OR:0.60, Cl:0.11-3.24). The rates of not serious AEs as asthenia and fatigue (ESPs:18.9%, control:13%) was lightly different in two groups (OR:1.51, Cl:0.66-3.45). Moreover, the rate of thrombocytopenia was not statistically different among the two groups (OR:5.13, Cl: 0.08-44.21) (Fig. 4).

We note that progression to AML was captured only for the formal study period. 2% of ESPs patients and 2.1% of control patients progressed to AML. The OR is not significant (OR:0.99, Cl: 0.16-6.21), presumably because of the low numbers of patients and events.

Discussion

The present meta-analysis in the treatment of anemia of MDS, using a comprehensive list of epoetin alfa and darbepoetin RCTs, demonstrated higher erythroid response rates. Significant efficacy of ESPS versus standard care or placebo controls in terms of Hb response (OR: 5.59, 95%CI: 2.74-11.42), the primary efficacy outcome in most of the studies reviewed.

The overall erythroid response rate (24%) found is higher to the modest efficacy of epoetin alfa observed in the first meta-analysis by Hellstrom-Lindberg et al. in 1995. 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. Another two meta-analyses about ESPs response in MDS patients were published 2007 and 2008. In the meta-analysis by Moyo et al was reported that response to ESPs was IWGc studies 57.6% and 31.6% non-IWGc studies ($p<0.001$) which is greater than present meta-analysis. But, in this meta-analysis were included also non-RCTs and maybe that is why the result differ. Moreover, Moyo et al study reported significantly higher erythroid response rates predominantly in the more recent studies that primarily utilized IWGc to define response which was not possible in the present study because not all RCTs followed the IWGc. In the Ross et al study the rate of responses was 32.1% in epoetin single-arm studies and 27.3% RCTs in which are similar to the results of present study.[22]

It has to be mentioned that there was only one darbepoetin RCTs and it makes difficult the analysis of epoetin versus darbepoetin response. In present meta-analysis the rates response in epoetin were higher than the rate of dabepoetin study. In contrast, in two meta-analyses, reported in 2006 and 2007, the response rates of drabepoetin are higher. In Mundle et al systematic review, with the use of standardized patient selection and response evaluation methods, epoetin alfa and darbepoetin alfa yielded comparable erythroid response rates in MDS patients. The epoetin groups achieved an Hb response rate of 57.6%, versus 59.4% for darbepoetin, but the difference was not statistical important ($p=0.828$).[31] And in the Ross et al review the major Hb response rate averaged 38.8% in darbepoetin studies, also higher than in the epoetin single-arm studies (24.5%) and EvC studies (11.4%).[22] This difference in findings is likely explained by different study eligibility criteria for each review, and until those details become available, interpretation remains difficult. Also, 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.

The evidence to date further suggests that a lower baseline erythropoietin level may be associated with a higher Hb response rate to ESPs. 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.[32] This is plausible because refractory anemia in the face of a high endogenous erythropoietin level may indicate relative non responsiveness of bone marrow. Conversely, anemia associated with a low serum erythropoietin level may respond more readily to exogenous ESPs. These observations are further supported by the findings of other ESP studies.[32,33,34] where in a lower serum erythropoietin level was associated with a greater Hb response rate to ESPs. These post hoc observations should be studied prospectively to determine if serum erythropoietin level could serve as a reliable guide to selection of MDS patients for ESP treatment. In present analysis, baseline erythropoietin level data were extractable only in one RCTs, so it could be analyzed. Mundle‘s et al meta-analysis supports

that lower mean baseline serum erythropoietin level associated with higher response rate in the epoetin alfa IWGc studies (p=0.007), because the percentage of transfusion-dependent patients was significantly higher in non IWGc studies where response rates were lower as well.

The results of this meta-analysis also suggest that ESP treatment for a longer duration and the use of concurrent iron may not associated with a higher frequency of Hb response (little difference). These findings are in contrast with the previous review. So, further studies should be conducted in order to elucidate if these factor enhance efficiency of ESPs in MDS. As do extended dose regimens that may enhance convenience, adherence, and efficacy of long-term regimens.

As for the other efficacy outcomes of interest as percentage of patients transfused, the rate of ESPs group (49.3%) was significant lower than control group (68.6%). It is suggested that QoL improves in ESP-treated patients, and this improvement is of a magnitude that is clinically meaningful. 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.[35] It is not unreasonable to speculate that ESAs, by reducing transfusion dependency and correcting anemia, may positively impact survival. But the available evidence is less compelling than for Hb response outcomes, because only 2 studies had extractable data.

As it's known from literature, granulocyte-colony-stimulating factor (G-CSF) and granulocyte macrophage-colony-stimulating factor (GM-CSF) increase neutrophil counts, do not increase the risk for leukemia, and have no effect on survival.[36] In present study, the results are similar. The concurrent treatment with G-CSF or GM-CSF isn't associated with higher Hb response compare to studies which did use concurrent treatment. So, the use of ESPs as monotherapy or in combination with G-CSF, is associated with improved survival. This is plausible considering the possible impact of transfusion and related iron overload on survival in MDS patients

As for the safety of ESPs, AEs rates were generally low in all studies and in one study none AE reported. Percentage of total AEs, serious and fatal AEs were even higher in the control group. Moreover, selected AEs, thrombocytopenia, asthenia and fatigue were more in ESPs group but the difference has not statistical important. Although, concerns have been raised previously about the danger of progression to AML due to these agents, ESPs has not been associated with higher rates in present study. In none study, ant death was attributed in ESPs. 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.[37] Whether there are differences in safety among ESPs, and whether ESPs will be proven to be safe with the long-term use that may be needed in MDS, remain to be seen. Only comparative, long-term follow-up trials will resolve these questions.

Conclusion

In this meta-analysis, the RCTs included comprise the best available evidence on the efficacy and safety of ESPs in the treatment of anemia associated with MDS. Patients with MDS treated with ESPs showed significantly higher erythroid response rates over time. Although the evidence for darbepoetin is sparse, thus far it appears that darbepoetin is as effective as epoetin. Random controlled trials of darbepoetin versus standard care or placebo controls are needed to establish not only the efficacy and safety, but also the costs and health care use associated with these treatment alternatives. Head-to-head trials of epoetin versus darbepoetin are also needed to compare Hb response in comparable patients using comparable response criteria, as well as QoL and other efficacy measures of potential interest, such as safety, long-term benefit, long-term survival, relapse rates, and AML progression.

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