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Epoetin alfa for the treatment of myelodysplastic syndrome-related anemia: A review of clinical data, clinical guidelines, and treatment protocols

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ABSTRACT

Myelodysplastic syndromes (MDS) are characterized by ineffective hematopoiesis, leading to hematopoietic precursor cell apoptosis and peripheral blood cytopenias. Anemia is the most frequently experienced cytopenia and is the main cause of MDS symptoms, with fatigue and dyspnea contributing to reduced quality of life and increased morbidity. As MDS disease course and prognosis is influenced by disease factors, prognostic scoring systems have been developed for MDS to aid clinical and therapeutic decisions following diagnosis. Erythropoiesis- stimulating agents (ESAs) have been used for many years to treat anemia in patients with lower-risk MDS without chromosomal abnormalities. The use of ESAs is recommended by international clinical practice guidelines, due to the large body of evidence demonstrating their effectiveness in lower-risk MDS. In March 2017, the European Medicines Agency approved epoetin alfa for the treatment of anemia in lower-risk MDS patients, based on the results from a Phase 3 clinical trial and three European registry studies. The effectiveness of biosimilar epoetin alfa (Binocrit®, Sandoz) to correct anemia in lower-risk MDS patients has also been demonstrated in a retrospective, single-center, observational study. The recent approval of epoetin alfa by the EMA in this setting will provide clinicians with a welcome, approved treatment option for lower-risk MDS.

1. Introduction

Myelodysplastic syndromes (MDS) comprise a highly heterogeneous group of clonal hematological neoplasms that arise from hematopoietic stem cells [1]. The annual incidence rate of MDS in the general population has been reported as 3.3 and 4.0 cases per 100,000 people in the US and Europe, respectively [2,3]. MDS are more common in men than women, and incidence rises with age; with an estimated incidence of 40–50 cases per 100,000 people aged ≥70 years in Europe [3]. Reported incidence rates of MDS vary considerably but appear to have increased over time, which may reflect a growing awareness of reporting requirements following the worldwide implementation of the International Classification of Diseases for Oncology (ICD-O-3) in 2001 [4].

MDS are characterized by ineffective hematopoiesis, leading to apoptosis in hematopoietic precursor cells and peripheral blood cytopenias [1,5]. Peripheral blood cytopenias experienced by lower-risk MDS International Prognostic Score System (IPSS low and intermediate-1) patients include anemia, neutropenia, and thrombocytopenia [6]. Anemia is the most common cytopenia, affecting > 50% of patients at presentation [7] and up to 90% of patients at some point during the course of the disease [8]. Anemia is the main cause of MDS symptoms, including fatigue and dyspnea, which result in a reduction of quality of life (QoL), and increased morbidity such as cardiac complications [9].

Progression to acute myeloid leukemia (AML) is a substantial risk, especially in MDS categorized as high-risk according to IPSS classification (IPSS high and intermediate-2) [10]. High-risk MDS patients have a reduced life expectancy and therefore initial treatment focuses on modifying the disease course using high-intensity therapies such as allogeneic bone marrow transplantation, chemotherapy, or hypomethylating agents [11,12]; treatment of symptoms in high-risk cases is a secondary concern.

The primary treatment aim in lower-risk MDS is correction of cytopenias, particularly anemia, to reduce symptoms and improve QoL [11,13,14]. Until recently, red blood cell (RBC) transfusions were the only first-line treatment approved for the correction of anemia in lower-risk MDS without cytogenetic abnormalities such as isolated deletion of

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chromosome 5q (del[5q]) [10]. For more than 20 years, erythropoiesis-stimulating agents (ESAs) have been available for the treatment of anemia associated with chemotherapy and chronic kidney disease. ESAs have also been routinely used off-label (in Europe and outside of Europe) as a treatment for anemia in lower-risk MDS patients without del(5q) [6,11,15]. Furthermore, international clinical guidelines have recommended the use of ESAs in lower-risk MDS patients without del (5q), due to the large body of evidence demonstrating their effectiveness in this setting [5,10,16].

In March 2017, the first ESA (Eprex®/Erypo® [epoetin alfa, Janssen-Cilag International]) was approved by the French health authority (National Security Agency for Medicines and Health Products) for the treatment of symptomatic anemia in adults with low- or intermediate-1 -risk MDS with low serum erythropoietin (< 200 mU/mL), based primarily on data from the EPOANE trial. Approval in other European countries was subsequently granted under the European Medicines Agency's (EMA) mutual recognition procedure [17]. This article aims to provide a review and analysis of epoetin alfa as a treatment of anemia in lower-risk MDS patients, as well as exploring clinical guideline recommendations.

2. Genetics and diagnosis of MDS

Diagnosing MDS can be challenging as patients are often asymptomatic and the disease morphology is non-specific, especially in its early stages [1]. For example, anemia is commonly observed in the elderly and is often unrelated to a hematological problem [21]. The diagnosis of MDS relies on detailed assessment of bone marrow and peripheral blood cytological composition using hematological techniques. Diagnosis is usually established by the identification of abnormal cell morphology (dysplasia) in peripheral blood and bone marrow aspirate, and assessment blast cell percentage [1]. In addition, chromosomal abnormalities are present in approximately 50% of MDS patients, and are often used in the diagnosis of MDS [18,19]. Deletion in the long arm of chromosome 5, known as del(5q), is the most common chromosomal alteration, observed in approximately 15% of MDS cases [18,20].

A number of morphological classifications exist to categorize patients with MDS. A diagnostic classification for MDS was first proposed by the World Health Organization (WHO) International Working Group (IWG) in 2001 [22], which was subsequently updated and expanded in 2008 [23]. The term 'therapy-related myeloid neoplasm' was subsequently proposed by WHO, to encompass disorders previously described as therapy-related MDS and AML [24]. In 2016, WHO classification for myeloid neoplasms and acute leukemia was revised to include recent clinical, prognostic, and genetic advances [25].

According to the most recent WHO classification, MDS can be categorized into one of six groups at diagnosis, based on a number of criteria including: the number of lineages presenting dysplastic features, the number of cytopenias in the peripheral blood, the presence or absence and percentage of ring sideroblasts, the percentage of blasts in the peripheral blood and bone marrow, karyotype and, when required, molecular genetics. The six MDS categories are: MDS with single-lineage dysplasia; MDS with multi- lineage dysplasia; MDS with ring sideroblasts, comprising two subtypes (single-lineage dysplasia and multi-lineage dysplasia); MDS with isolated del(5q); MDS with excess blasts; and unclassifiable, including three categories (1% peripheral blood blasts, single-lineage dysplasia and pancytopenia, and with a defining cytogenetic abnormality related to myelodysplasia) [25].

Following advances in cytogenetic and molecular markers, prognostic categorization for pre-MDS conditions have recently been proposed [26]. The classification was developed to define potential pre-MDS conditions, which may develop into MDS or other hematopoietic neoplasms; or alternately, have no further clinical manifestations. The proposed categories include low- and high-risk MDS, in addition to four pre-MDS conditions; idiopathic cytopenia of undetermined significance, idiopathic dysplasia of undetermined significance, clonal hematopoiesis with indeterminate potential; and clonal cytopenia of undetermined significance. Categorization into one of these groups is based on the following criteria: monoclonal/oligoclonal, dysplasia; cytopenia (s),bone marrow blasts, flow abnormalities, cytogenetic abnormalities, and molecular aberrations [26].

3. Prognostic risk classification

Disease course and prognosis is influenced by disease factors such as the number of cytopenias, marrow blast cells, and cytogenetic abnormalities [6,27]. Patient-related factors are also involved, with poorer outcomes reported in patients that are male, elderly, or with comorbidities [28–30]. Several prognostic scoring systems based on risk stratification have been developed for MDS to aid clinical and therapeutic decisions following diagnosis [28,31,32]. Recommended treatment strategies are also based on these definitions of risk [16]. Greenberg et al proposed the IPSS, which categorizes MDS patients into one of four risk groups, predictive of patient survival and disease progression to AML; low (score 0), intermediate-1 (score 0.5–1.0), intermediate-2 (score 1.5–2.0), or high (score ≥2.5) [31]. The prognosis classification is based on the presence or absence of multi-lineage cytopenias, abnormal bone-marrow cytogenetics, and increased bone-marrow blast counts. The IPSS became an important standard for assessing prognosis in untreated MDS patients, and its manageability and reproducibility meant it was widely adopted in clinical studies [1,32].

In 2012, the classical IPSS scoring system was revised to incorporate additional marrow blast categories, refine the cytogenetic abnormality groups, include evaluation of cytopenia depth, and include differentiating features (such as patient age, performance status, and serum ferritin). The revised model was based on analysis of data from over 7,000 patients with untreated MDS and identified five major prognostic groups; very good, good, intermediate, poor, very poor [32]. The revised IPSS (IPSS-R) categories show strong correlation with median survival and median time to AML transformation (Table 1). In the patient cohort studied, median survival ranged from 8.8 years in the very good prognostic group to 0.7 years in the very poor group. Time to AML progression was 10.8 years in the low-risk group, compared with 0.7 years in the very high-risk group [32].

Malcovati et al defined a WHO classification-based prognostic scoring system (WPSS) for predicting survival and AML progression of MDS patients [28]. Five risk groups were identified based on WHO category, karyotype according to the IPSS genetic categories, and transfusion requirement; very low (score 0), low (score 1), intermediate (score 2), high (score 3–4), and very high (score 5–6). The WPSS prognostic scoring system was demonstrated to provide an accurate prediction of survival and risk of leukemic evolution at any time during the MDS disease course [28]. In a cohort of MDS patients diagnosed between 1982 and 2004, the median survival was 11.8 years in very low-risk patients, compared with 8 months in very high-risk patients. The risk of progression to AML within 5 years was 3% in the very low-risk group, compared with 84% in the very high-risk group [28].

However, as advances in flow cytometric analysis, gene expression profiling, and array-based genomics improve our understanding of MDS pathogenesis and prognosis, it is expected that the current prognostic scoring systems will require further refinement in the future [33].

4. Mechanisms of anemia in MDS patients

Anemia in MDS patients is caused by ineffective erythropoiesis due to an impaired response to endogenous erythropoietin. However, the mechanisms behind this impaired response have not yet been fully elucidated. One suggestion is that erythropoietin receptors in the bone marrow of MDS patients are structurally defective, leading to altered receptor signaling upon erythropoietin binding [9,34]. Alternatively, it has been suggested that premature hematopoietic precursor apoptosis occurs in MDS, caused by a defect in erythropoietin-induced

Table 1
IPSS-R prognostic risk category clinical outcomes [32].

	No. of patients	Very low	Low	Intermediate	High	Very high
Patients, %	7,012	19	38	20	13	10
Survival, all* (95% CI)		8.8	5.3	3.0	1.6	0.8
		(7.8–9.9)	(5.1–5.7)	(2.7–3.3)	(1.5–1.7)	(0.7–0.8)
Hazard ratio (95% CI)		0.5	1.0	2.0	3.2	8.0
		(0.46–0.59)	(0.93–1.1)	(1.8–2.1)	(2.9–3.5)	(7.2–8.8)
Patients, %	6,485	19	37	20	13	11
AML/25%*†		NR	10.8	3.2	1.4	0.73
(95% CI)		(14.5–NR)	(9.2–NR)	(2.8–4.4)	(1.1–1.7)	(0.7–0.9)
Hazard ratio		0.5	1.0	3.0	6.2	12.7
(95% CI)		(0.4–0.6)	(0.9–1.2)	(2.7–3.5)	(5.4–7.2)	(10.6–15.2)

AML, acute myeloid leukemia; CI, confidence interval; IPSS-R, Revised International Prognostic Scoring System; NR, not reached.
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* Median, years, $P < 0.001$.

† Median time to 25% AML evolution, $P < 0.001$.

antiapoptotic pathways and by stimulation of proapoptotic signals. This mechanism is supported by a number of early studies that demonstrated that the bone marrow of MDS patients contains a higher number of apoptotic cells compared with controls [35–37]. There is also evidence to suggest that increased production of tumor necrosis factor alpha and interferon gamma by bone marrow macrophages are involved in hematopoiesis inhibition in MDS [38].

5. ESA treatment for anemia in lower-risk MDS patients

ESAs include epoetin alfa, epoetin beta, epoetin zeta, epoetin theta, and long- acting darbepoetin alfa. ESAs have been widely used in lower-risk MDS patients without a del(5q) chromosome abnormality for the treatment of anemia, even prior to the recent approval of epoetin alfa in this indication, leading to improvements in QoL and avoidance of blood transfusions [5,6]. The efficacy of ESAs in lower-risk non-del(5q) MDS has been demonstrated in clinical trials involving over 2500 patients and several meta-analyses [9]. As a result, the use of ESAs in this setting has been recommended for many years by well-established clinical practice guidelines [5,10,16,39,40] and ESAs are generally accepted as the first-line treatment for lower-risk non-del(5q) MDS [41].

Limited data are available on the effectiveness of ESAs for the treatment of anemia in lower-risk patients with del(5q), although lower response rates and shorter response durations have been reported in del (5q) MDS in comparison with non-del(5q) MDS [6,42]. In patients treated with erythropoietin or darbepoetin (± granulocyte colony-stimulating factor [G-CSF]), the therapy response rate (according to IWG 2006 criteria) was 39% in patients with del(5q), compared with 52% in patients with non-del (5q) ($P = 0.10$). Furthermore, the mean duration of response was 13 months and 27 months in del (5q) and non-del(5q) patients, respectively ($P = 0.003$) [42]. Patients with higher- risk MDS are generally not considered for ESA therapy because of poor responses, short survival times, and the frequent use of hypomethylating agents and stem cell transplantation, which require RBC transfusion support.

A number of clinical and biological factors have been shown to be predictive of ESA therapy response in MDS patients, including: short duration of disease [9]; low or no RBC transfusion requirement (< 2 units/month) [9,11,43,44]; baseline serum erythropoietin level (reported predictive levels range from < 100 to < 500 U/L) [9,11,43,44]; no or limited excess of bone-marrow blasts (< 10%) [9,11,45]; IPSS low or intermediate-1 [9,11]; refractory anemia diagnosis [9]; normal karyotype [9]; absence of multilinear dysplasia [11]; and WHO subtypes RA (refractory anemia) and RARS (RA with ring sideroblasts) [45]. This last point is controversial as the data for RARS are unclear. In a meta-analysis performed by Moyo et al, RA and RARS patients were pooled together and the presence of either was predictive of higher response rates [45]. However, an earlier meta-analysis reported response rates in RARS patients specifically to be significantly lower than in other MDS patients [46]. Subsequent studies have found epoetin combined with G-CSF to be particularly effective in RARS patients [47,48], although others have reported no additional benefit of adding G-CSF [11,49].

Factors shown to be associated with a longer duration of ESA response include major response according to WHO IWG 2000 criteria, IPSS low to intermediate-1, bone-marrow blasts less than 5%, and absence of multilineage dysplasia [11]. There is some evidence to suggest that early intervention with ESAs (within 6 months) is associated with a better treatment response in terms of response rate and duration of response [11,50].

Two mechanisms have been proposed to explain ESA therapy response in over 50% of MDS patients [9]. The first is that ESAs may inhibit apoptosis and promote the production of erythrocytes and erythroid progenitor survival, leading to proliferation, maturation, and restored erythropoiesis of the MDS clone [9]. The second hypothesis suggests that ESAs may stimulate polyclonal erythropoiesis by promoting the survival of residual, karyotypically normal erythroid precursors. Rigolin et al reported that patients responsive to recombinant human erythropoietin therapy had a higher number of cytogenetically normal bone marrow erythroid cells (representing residual normal erythroid cells) at diagnosis, compared with non-responsive patients [51]. This proposal could also account for a lack of response to ESA therapy in some patients; karyotypically abnormal clonal erythroid precursors may be predominant in the bone marrow, which are unable to respond to endogenous and therapeutic exogenous erythropoietin [51].

6. Review of epoetin alfa clinical data in MDS

Moyo et al conducted a systematic review and meta-analysis of studies carried out between 1990 and 2006, which aimed to assess ESA response rates in patients with MDS treated with epoetin alfa as monotherapy [45]. A total of 925 patients receiving epoetin alfa were evaluable for ESA response; the analysis included 589 patients from 9 studies that used IWG criteria (IWGc) to define response and 336 patients from 13 non-IWGc studies. For IWGc studies, response was defined as major (i.e. increase of > 2 g/dL in hemoglobin level from baseline in patients with a hemoglobin of ≤11 g/dL or transfusion independence for transfusion-dependent patients) or minor (i.e. increase of 1–2 g/dL in hemoglobin level from baseline in patients with hemoglobin ≤11 g/dL or 50% reduction in transfusion requirements for transfusion-dependent patients). For non-IWGc studies, hematologic response rate definitions varied and included favorable, complete, and partial response.

Overall ESA response rates for epoetin alfa studies using IWGc are shown in Fig. 1. The pooled estimate of response rate for epoetin alfa

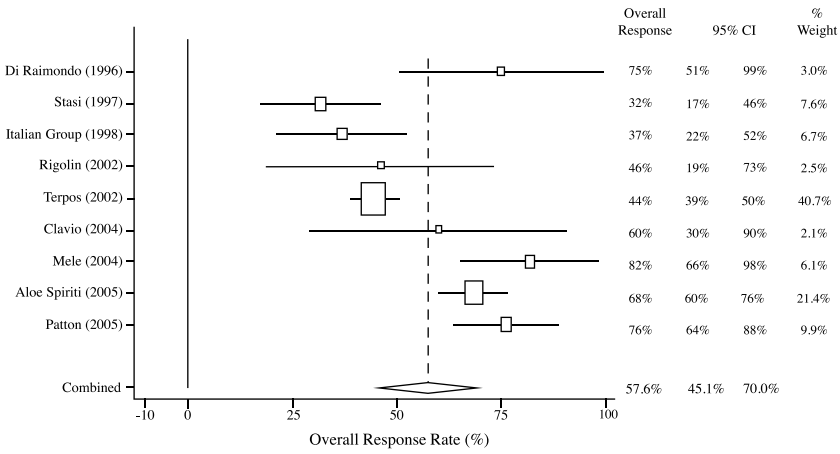

Fig. 1. Overall erythroid response rates for studies using IWGc [45].
CI, confidence interval.
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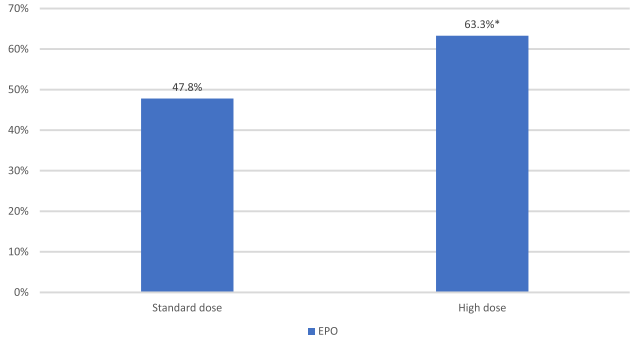

Treatment	Standard dose/week	High dose/week
Epoetin alfa, units (n)	30,000–40,000 (5)	60,000–80,000 (4)
Note: *p<0.001 compared to respective standard dose.		

Fig. 2. Response rates for standard and high doses of epoetin alfa [45].
* P < 0.001 compared with respective standard dose.
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was significantly higher for IWGc studies compared with non-IWGc studies (57.6% vs 31.6%; P < 0.001). As shown in Fig. 2, studies that used standard weekly doses of epoetin alfa showed a significantly lower response rate (47.8%) compared with studies using higher dosing regimens (63.3%; P < 0.001) [45]. The same meta- analysis found no significant difference in pooled response rate for epoetin alfa and darbepoetin alfa (57.6% vs 59.4%, p = 0.828). A more recent systematic review has also reported no clear differences between epoetin alfa and darbepoetin alfa [52].

EPOANE 3021 was an international, randomized, double-blind, placebo- controlled, multicenter study, which assessed the efficacy and safety of epoetin alfa (Eprex®/Erypo®) in patients with lower-risk MDS suffering from symptomatic anemia [53]. Eligible patients had: *de novo* IPSS low or intermediate-1 MDS; hemoglobin ≤10.0 g/dl; ≤4 RBC unit transfusions within 8 weeks prior to randomization; and baseline serum erythropoietin < 500 mU/mL. The primary endpoint was improvement in anemia outcome up to Week 24, evaluated by erythroid response, based on IWG 2006 criteria [12]. In total, 130 patients were randomized 2:1 to weekly subcutaneous epoetin-alfa 450 IU/kg (n = 85) or placebo (n = 45) [53].

The primary endpoint was met as the proportion of patients achieving erythroid response up to Week 24 was significantly higher in the epoetin alfa group compared with placebo (31.8% vs 4.4%, P < 0.001) [53]. At Week 24, erythroid response rate was significantly higher in the epoetin alfa group compared with placebo, by both investigator evaluation (36.5% vs 4.4%, P < 0.001) and independent response review committee evaluation (27.1% vs 2.2%, P < 0.001) [49]. Furthermore, compared with placebo, epoetin alfa induced a sustained erythroid response and significantly prolonged the time to RBC transfusion (Table 2).

An *ad- hoc* analysis demonstrated that significant improvements in QoL scores were observed at Week 24 in epoetin alfa treated responders, compared with non- responders (Functional Assessment of Cancer Therapy – Anemia [FACT-An] score, P = 0.025; EQ-5D, P = 0.007) [54]. No new safety signals were detected; safety data were comparable up to Week 24 for epoetin alfa and placebo and progression to AML was similar between groups (3.5% epoetin alfa vs 4.4% placebo) [54]. Results from this Phase 3 study formed the basis of the approval in Europe of Eprex®/Erypo® in lower-risk MDS-related anemia [17].

Table 2
Secondary endpoints of the EPOANE 3021 study [54].

	Epoetin alfa (N = 85)	Placebo (N = 45)	P-value
Mean duration of erythroid response, up to Week 52, days (SD)	192.3 (88.92)	99.0 (69.30)*	
Maintained response from Week 24 to Week 48, %	9.4 (n = 8)	N/A (no patients completed up to Week 48)	
Median time to first RBC transfusion, days	49	37	0.046
Median time to first RBC transfusion after Week 4, days (*ad hoc* analyses)	142.0	50.0	0.007
Mean number of transfusion-free days (95% CI)	212.4 (182.9–241.9)	176.1 (156.9–195.4)	
Patients requiring RBC transfusion between Week 16 and Week 24, % (N)	24.7 (19)	54.1 (20)	

CI, confidence interval; RBC, red blood cell; SD, standard deviation.
* The placebo group result is based on data from two patients and therefore, statistical and clinical significance should not be made.

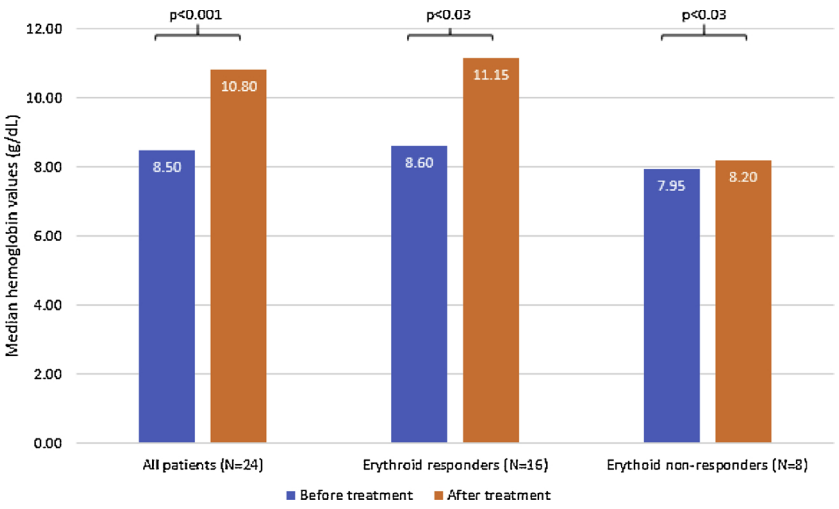

Fig. 3. Biosimilar epoetin alfa retrospective analysis – hemoglobin levels [55].
Reprinted by permission from RightsLink on behalf of Springer Nature: Springer Nature, Annals of Hematology, Biosimilar epoetin in elderly patients with low-risk myelodysplastic syndromes improves anemia, quality of life, and brain function, Castelli, et al., [COPYRIGHT] 2014.

A retrospective, single-center, observational study has assessed the efficacy of biosimilar epoetin alfa (Binocrit®, Sandoz) in lower-risk MDS patients with anemia [55]. Patients eligible for inclusion were aged ≥65 years, with newly diagnosed non-del(5q) MDS (IPSS score < 1.5) and at least one cytopenia. The primary endpoint was erythroid response according to IWG criteria 2006 [12] and blood transfusion requirement. Patients received weekly subcutaneous biosimilar epoetin alfa (40,000 IU) for a minimum of 12 weeks and those with erythroid response continued treatment for an additional 12 weeks [55].

Of the 24 included patients, 16 (66.7%) patients achieved an erythroid response and 15 (62.5%) became transfusion-independent. Two patients had a reduction in transfusion requirements (at least 4 RBC units over 8 weeks, compared with the transfusion requirement prior to treatment) and 7 (29.1%) patients were non-responders (transfusion independence or a reduction in transfusion requirement was not achieved). Hemoglobin values were significantly higher following biosimilar epoetin alfa treatment compared with levels before treatment (median hemoglobin 10.80 g/dl vs 8.50 g/dl, P < 0.001), with responses maintained for 24 weeks. As shown in Fig. 3, this pattern was also observed in subgroups of erythroid responders and non-responders [55].

Erythroid response was significantly correlated with an improvement in FACT-An score and there was a statistically significant positive correlation between mini-mental state examination evaluation score and hemoglobin value, indicating erythroid response is associated with improvements in cognitive status [55].

7. Guideline recommendations for ESA use in MDS

Guideline recommendations on the use of ESAs for the treatment of anemia in patients with MDS have been produced by the National Comprehensive Cancer Network (NCCN), the European Society of Medical Oncology (ESMO), and European LeukemiaNet.

The NCCN clinical practice guidelines on MDS recommend ESAs for the treatment of symptomatic anemia in patients with lower- risk MDS without the del(5q) mutation, who have an erythropoietin level ≤500 mU/mL [16]. In lower-risk patients with del(5q), the NCCN guidelines recommend lenalidomide but also allow consideration of an initial trial of ESA therapy in cases where serum erythropoietin levels are ≤500 mU/mL [16].

The recently updated ESMO guidelines for the management of anemia in cancer patients includes management of MDS patients [56]. This guideline recommends that ESA therapy should be considered in MDS patients with: symptomatic anemia; Hb < 10 g/dL; low to intermediate-1 risk (IPSS) or very low to intermediate risk (IPSS-R); less than two RBC transfusions per month and/or serum EPO < 500 IU/L (note that the EMA-approved indication for epoetin alfa includes a serum EPO level of < 200 IU/L). An initial weekly subcutaneous dose within the range of 30,000–80,000 IU is recommended for recombinant human erythropoietin [56]. In patients who are unresponsive to treatment after 8–12 weeks, the addition of G-CSF is recommended. Finally, the guideline suggests that RBC transfusions or investigational medicines should be considered as second-line treatment in patients with non-del (5q) MDS and lenalidomide in patients with del(5q). A summary of the current NCCN and ESMO treatment algorithms for anemia management in patients with very low to intermediate-risk MDS is provided in Fig. 4.

The European LeukemiaNet guidelines recommend that patients with IPSS low- or intermediate-1-risk, with moderate-to-severe anemia (hemoglobin < 10 g/dL), serum erythropoietin level < 500 mU/mL, and/or RBC transfusion requirement < 2 U/month be considered for therapy with epoetin alfa or beta at an initial dose ranging from 30,000–60,000 IU/week [5]. Those patients who do not respond to epoetin alone after 8 weeks of treatment should be given G-CSF (300 mg/week in 2–3 divided doses) in combination.

8. Discussion

Anemia is the most frequent cytopenia affecting patients with MDS. ESAs have been shown to effectively treat anemia in patients with lower-risk MDS without chromosomal abnormalities, and are recommended in major clinical guidelines, although approval of an ESA in this setting has been granted only recently in Europe. A growing body of evidence has defined pre-treatment variables that predict a clinically relevant response to ESA treatment.

Although the majority of clinical studies evaluating ESAs in lower-risk MDS patients have involved epoetin alfa, the effectiveness of other ESAs in this setting has also been demonstrated. Clinically relevant responses have been reported from a number of studies evaluating epoetin beta [57,58], darbepoetin alfa [45,59–63], and epoetin zeta [64] for the treatment of anemia in lower-risk MDS patients.

There is increasing evidence for the effectiveness of ESAs for the treatment of MDS-related anemia, partly due to the generation of data from recent European clinical studies in lower-risk MDS patients and the inclusion of ESAs in international clinical guidelines. Following the recent EMA approval of epoetin alfa to treat anemia in lower-risk MDS, ESAs provide a welcome, approved treatment option for clinicians.

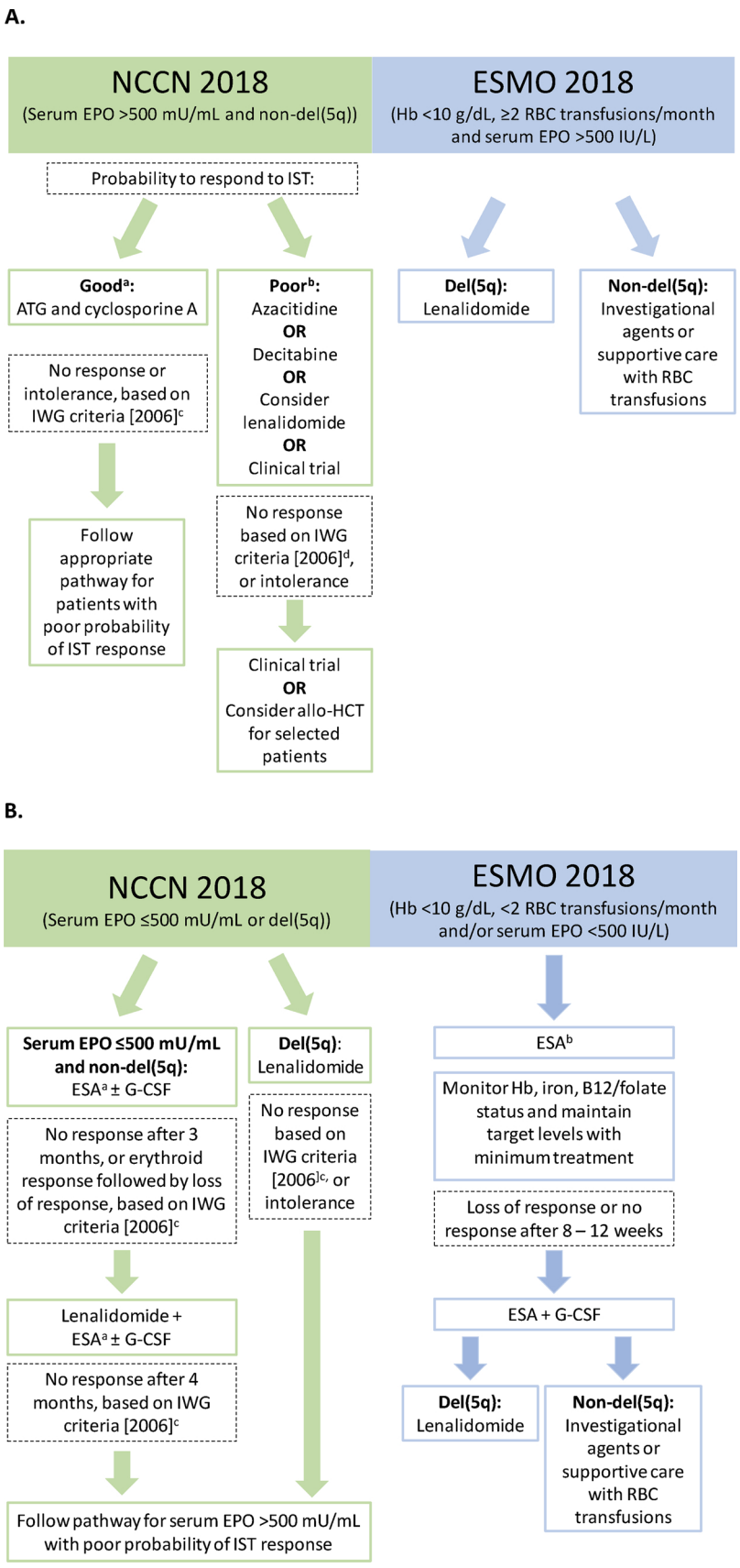

Fig. 4. Summary of the latest NCCN and ESMO treatment algorithms for very low to intermediate-risk MDS, for patients with symptomatic anemia and serum erythropoietin > 500 mU/mL (A) or ≤500 mU/mL (B).
[a]Good probability to respond: patients generally ≤60 years, ≤5% marrow blasts or those with hypocellular marrows, HLA-DR15 positivity, PNH clone positivity, or STAT-3 mutant cytotoxic T cell clones. IST includes equine ATG +/- cyclosporin A. [b]Poor probability to respond: patients lacking features listed in footnote a. [c]Failure would be considered if no response within 3–6 months. [d]No response within 6 cycles of azacytidine or 4 cycles of decitabine.
[a]Epoetin alfa or darbepoetin alfa. [b]ESA-treated patients who are iron deficient and transfusion independent may be considered for intravenous iron treatment. [c]Failure would be considered if no response within 3–6 months.
ATG, anti- thymocyte globulin; del(5q), deletion of chromosome 5q; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; ESMO, European Society of Medical Oncology; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HLA, human leukocyte antigen; IST, immunosuppressive therapy; IWG, International Working Group; MDS, myelodysplastic syndromes; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; STAT3, signal transducer and activator of transcription 3.

Declarations of interests

AK and NM are current or previous employees of Sandoz Biopharmaceuticals, HEXAL AG, Holzkirchen, Germany. PG has acted as an advisor to Sandoz Biopharmaceuticals. MA has acted as a consultant to Amgen, Accord, Hospira, JnJ, Novartis, Pfizer, Roche, Sandoz Biopharmaceuticals, Teva. MA has also received honoraria for lectures at symposia of Chugai, Kirin Kyowa.

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