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ORIGINAL ARTICLE

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Biosimilar erythropoiesis-stimulating agents are an effective and safe option for the management of myelofibrosis-related anemia

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Abstract

Objectives: Erythropoiesis-stimulating agents (ESA) have an established role in treating anemia in hematological malignancies. However, their role, particularly biosimilar ESA (B-ESA), in myelofibrosis (MF) is not well established.

Methods: This study retrospectively collected data on 96 MF patients treated with B-ESA (alpha/zeta) for the management of anemia to assess safety, efficacy (anemia response [AR]), and survival.

Results: Seventy-seven patients (80%) obtained AR. The median time to AR was 2.5 months. In multivariate analysis, significant predictive factors of AR were transfusion independency ($p = .006$) and ferritin levels <200 ng/ml ($p = .009$) at baseline. After a median follow-up of 43.8 months from diagnosis, 38 patients (39%) died, 11 (28.9%) from leukemic evolution. Only two patients (2.5%) stopped B-ESA for toxicity. The 24-month survival was significantly affected by response to B-ESA (70.8% in AR vs. 55.3% in non-responder patients, $p = .016$). In multivariate analysis, age ≤ 70 years ($p = .029$) and Hb > 8.5 g/dl ($p = .047$) at baseline were significantly associated with improved survival, with a trend for longer survival in AR patients ($p = .06$).

Conclusions: B-ESA seems to be an effective and well-tolerated option for anemia treatment in the MF setting. This strategy deserves further clinical investigation.

KEYWORDS
anemia, biosimilar pharmaceuticals, erythropoiesis-stimulating agents, Janus kinase inhibitors, myelofibrosis, outcome

Novelty statements

What is the new aspect of your work?

We evaluated biosimilar erythropoiesis-stimulating agents (B-ESAs) in patients with myelofibrosis (MF).

What is the central finding of your work?

Most patients obtained an anemia response and tended to have improved survival showing that B-ESAs were an effective and well-tolerated option in MF.

What is (or could be) the specific clinical relevance of your work?

Early B-ESA treatment before transfusion dependency develops should be considered.

1 | INTRODUCTION

Myelofibrosis (MF) is a rare clonal neoplastic disease characterized by bone marrow fibrosis, palpable splenomegaly, and a range of severe constitutional symptoms that can include night sweats, unexplained fever, abdominal pain, and weight loss.[1–3] Cytopenias, particularly anemia and thrombocytopenia, are frequently encountered in patients with MF.[2,3] Anemia is the more frequent manifestation of MF: nearly 40% of MF patients have hemoglobin (Hb) levels <10 g/dl at diagnosis, and about 25% of them are transfusion-dependent. Anemia has consistently been associated with worsening patient-reported quality of life and a negative impact on MF prognosis.[3,4] The pathogenesis of MF-related anemia is multifactorial and includes bone marrow failure with ineffective erythropoiesis, resulting in extramedullary hematopoiesis and reduced survival of red blood cells (RBC); sometimes, iron, vitamin B12, or folate deficiency is found, whereas autoimmune hemolysis or bleeding are rare.[5] Moreover, cytoreductive therapy (e.g., hydroxyurea or Janus kinase [JAK] inhibitors) may further exacerbate MF-related anemia.[6]

Although erythropoiesis-stimulating agents (ESA) have been used successfully in the management of anemia in several hematological malignancies, their role in MF is not as well established.[7] Diverging results have been reported in the few published studies, with anemia response (AR) rates ranging from 16% to 85%.[8–13]

In the pivotal COMFORT-I study,[10] the use of ESA was discouraged due to concerns regarding possible activation of the JAK pathway, potentially counteracting the effects of ruxolitinib on reducing spleen size. However, the use of ESA in patients receiving ruxolitinib has been demonstrated to be safe and did not affect the efficacy of the drug in a post hoc analysis of the COMFORT-II trial and real-life multicenter experience.[9,11]

Several factors have been identified as predictors of response to treatment, but there is no agreement among the authors. The endogenous erythropoietin (EPO) level has been demonstrated to be a good predictor of response; on the other hand, the role of transfusion dependency is more controversial.[12,13]

To date, data are lacking on the use of biosimilar ESA (B-ESA) in the MF setting.

This study aims to evaluate the efficacy and safety of B-ESA alpha and zeta in the management of anemia in MF patients.

2 | METHODS AND MATERIALS

2.1 | Patients and study design

We retrospectively evaluated patients with an MF diagnosis at five Italian hematological centers who received B-ESA (alpha and zeta epoetin) between 2009 and 2021 in a real-life setting for at least 1 month to treat anemia (Hb ≤ 10 g/dl). Exclusion criteria for initiating B-ESA treatment were an estimated life expectancy of fewer than 6 months and concomitant therapy with other anemia-treating agents (steroids and danazol). B-ESA was given off-label with patient-informed consent.

All centers were asked to report, using an electronic case report form (e-CRF), their consecutive MF patients who received B-ESA according to standard clinical practice. Each Center reported the total number of medical files by data input into an electronic database developed to record all study data after anonymization of the patients with an alphanumeric code to protect personal privacy. Data collected included patient demographics, comorbidities, concomitant medications, clinical/laboratory tests at diagnosis, at the start of B-ESA and during follow-up, date of introduction and suspension of cytoreductive treatment and B-ESA, starting dose of B-ESA, and requirement for dose modifications over the time, and adverse events (AEs) related to B-ESA therapy. Also, thrombotic and hemorrhagic complications after the start of B-ESAs were collected. Details of the number of RBC transfusions were recorded throughout the study.

Any treatment decision was at the physician's discretion, independent of study participation. After the first data entry, the follow-up information was validated by revision of clinical data, and specific queries were addressed to the participating Center in case of inconsistent data.

All patients were followed until death or data cut-off.

This study was performed in accordance with the guidelines of the Institutional Review Boards of the participating centers and the standards of the Helsinki Declaration.

2.2 | Definitions

Diagnoses of primary MF (PMF) and post-polycythemia vera (PPV)/post-essential thrombocythemia (PET) MF were made according to World Health Organization criteria (WHO) at the time of diagnosis of MF or International Working Group on Myelofibrosis Research and

Treatment (IWG-MRT) criteria, respectively.[14,15] All patients who received treatment with B-ESA in the current analysis were in chronic phase (peripheral and marrow blast cells <10%).

The risk category was assessed at diagnosis, according to International Prognostic Score System (IPSS),[16] and at the start of B-ESA treatment, according to the Dynamic International Prognostic Score System (DIPSS).[17] Histologic examination was performed at local institutions; fibrosis was graded according to the European Consensus Grading System.[18] Unfavorable karyotype was categorized as previously described.[19] A diagnosis of leukemic transformation was made according to WHO criteria, with a 20% bone marrow or peripheral blood blast threshold for diagnosis.[15] Transfusion dependency was defined as the need for ≥2 RBC transfusions/month for at least 3 months.

2.3 | Treatment response

An anemia response (AR) was defined as a complete response (CR), according to the International Working Group – Myeloproliferative neoplasms Research and Treatment (IWG-MRT) criteria,[20] such as a rise in Hb values > 2 g/dl for transfusion-independent patients and becoming transfusion independent for transfusion-dependent patients. A partial response (PR) was reached with a reduction of ≥50% in transfusion requirement for transfusion-dependent patients or a sustained Hb increase between 1 and 2 g/dl in transfusion-independent patients. The non-responder (NR) group includes all other cases.

According to the type of erythroid response, the patients were divided into two subgroups: responders (AR, including CR and PR) and non-responder patients (NR).

2.4 | Toxicity and long-term outcome

All AEs during the ESA treatment were retrieved by the evaluation of medical charts reporting routine laboratory parameters and type/grade of AEs. Temporary and permanent ESA discontinuations at any time were also recorded. All AEs were defined and graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Specifically, events graded ≥2 required active systemic treatment, and those graded 4 were life-threatening. Outcomes measures included death and leukemic transformation.

2.5 | Statistical analysis

Statistical analysis was carried out at the biostatistics laboratory of Milano-Bicocca University. Continuous variables were summarized by their median and range (IR) and categorical variables by count and relative frequency (%) of each category. Comparisons of quantitative variables between groups of patients were carried out by a logistic regression model, and the association between categorical variables was tested by the Chi-squared test.

The development of response in time was analyzed in a survival analysis framework defining a "survival time from response" as time elapsed from treatment administration to achievement of response. Transplant or death before response was considered as censoring. The response rate was obtained as the ratio between the number of responses and the total person-time for analysis, with the 95% confidence interval (CI) according to the exponential model. The incidence probability in time of response was described by the Kaplan–Meier estimator. The impact of covariates on the rate (hazard) of response was assessed by the exponential model. Covariates with a significant impact on univariate models were considered in multivariate models.

The impact of response on the survival time was assessed, accounting for the response being achievable in time and reversible. This was accounted for by a data processing step with the definition of a time-varying response status, where subjects who will develop response are non-responders from treatment administration to the achievement of response, and responders from the achievement of response to the end of the follow-up or the loss of response. The rate of death in responders and non-responders was obtained as the ratio between the number of deaths and the total person-time for analysis, with the 95% CI and the test for comparison according to the exponential model. The survival probability in time in responders and non-responders was described by the Simon Makuch estimator with a 6-month landmark to gain an initial set at risk of responders.[21] Curves were compared by the Log Rank test. The impact of response status and further covariates on the rate (hazard) of survival was assessed by the Cox semi-parametric model. Covariates other than response were considered in univariate models, and covariates (including response status) with a significant impact on univariate models were considered in multivariate models.

3 | RESULTS

3.1 | Study population

A total of 96 consecutive patients affected by PMF ($n = 55$), PPV-MF ($n = 8$), or PET-MF ($n = 33$) fulfilled the inclusion criteria and were included in the analysis. The median age at the start of B-ESA treatment (baseline) was 75 years (IR 39–92); 17 patients (18%) were transfusion-dependent, and 20% belonged to the high-risk category according to DIPSS, while 64% and 16% were in the intermediate-2 and intermediate-1 category, respectively.

At baseline, the median Hb level was 9.0 g/dl (IR 7.0–10.0), the median ferritin value was 180 ng/ml (IR 6–2889), and the median endogenous EPO level was 48 U/L (IR 4–1742).

B-ESA was started after a median time from MF diagnosis of 13 months (IR 0–337). According to cytoreductive treatment, 59 patients (61%) received concomitant treatment with JAK2 inhibitors. Of them, 22 patients (37.3%) started B-ESA after a median time on ruxolitinib of 8.7 months (IR 3.0–70.4), 25 (42.4%) patients received B-ESA at the same time or within 3 months of ruxolitinib, and 12 (20.3%) patients before ruxolitinib start. Six patients (6.2%) subsequently underwent allogeneic stem cell transplantation (ASCT).

3.2 | Response to treatment

Patients received B-ESA for a median of 13.4 months (IR 1.4–107). Sixty-two patients (65%) received alpha B-ESA, and the remaining 34 patients (35%) were treated with zeta B-ESA. The median initial dose of B-ESA was 40 000 U/week subcutaneously, regardless of the type of B-ESA.

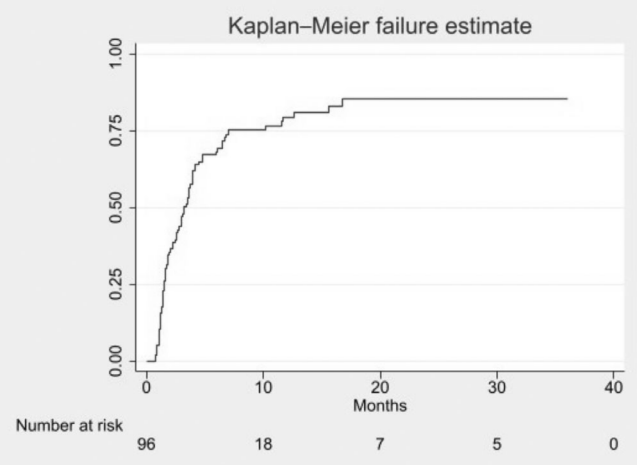


FIGURE 1 Estimate of the incidence probability of anemia response (AR) over time

At any time, 77 patients (80%) achieved an AR, of whom 64 obtained CR (67%) and 13 PR (13%), with an incidence rate of AR of 13 per 100 patients-month. The median time to AR was 2.5 months (IR 0.8–16.8), and most patients acquired AR within 12 months from baseline (79.4%, 95% CI: 70.3–87.2%; Figure 1). Conversely, 19 patients (20%) never achieved an AR during observation.

Baseline characteristics of the general population and responder and non-responder groups are summarized in Table 1. Patients who achieved an AR did not present significant differences compared to the NR group in the main biological features at baseline, except for a lower incidence of transfusion dependency ($p < .0001$), higher median Hb level ($p = .002$), lower median ferritin level ($p = .008$), and lower median EPO level ($p = .034$).

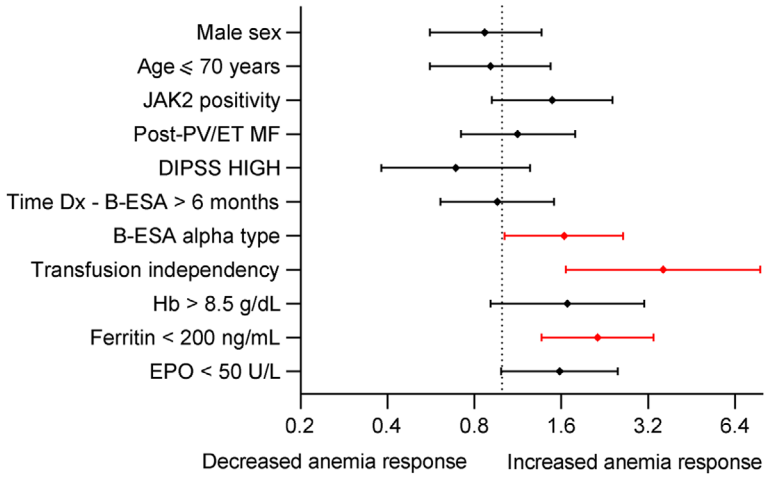
In univariate analysis, significant predictors of response were transfusion independency ($p = .001$), ferritin level < 200 ng/ml ($p = .001$) at baseline, and type alpha of B-ESA ($p = .041$), as reported in Figure 2.

Time to AR did not significantly differ when considering the initial dose schedule ($p = .29$). However, in nine patients (9.3%), the initial B-ESA dosage had been escalated due to an insufficient increase in

TABLE 1 Main characteristics of the general population, responders (AR), and non-responder patients (NR) at baseline

Characteristic	Overall ($n = 96$)	AR group ($n = 77$)	NR group ($n = 19$)	p
Median age (range)	75 (39–92)	75 (39–92)	73 (46–81)	.51
Male sex, no. (%)	49 (51.0)	39 (50.6)	10 (52.6)	.87
Primary MF, no. (%)	55 (57.3)	45 (58.4)	10 (52.6)	.64
Driver mutation status, no. (%)				.328
JAK2	62 (64.6)	53 (68.8	9 (47.4)	
MPL	7 (7.3)	6 (7.8)	1 (5.3)	
CALR	17 (17.7)	14 (18.2)	3 (15.8)	
Triple-negative	4 (4.2)	2 (2.6)	2 (10.5)	
Unknown	6 (6.2)	2 (2.6)	4 (21.0)	
DIPSS, no (%)				.07
Intermediate 1	15 (15.6)	15 (19.5)	0	
Intermediate 2	62 (64.6)	49 (63.6)	13 (68.4)	
High	19 (19.8)	13 (16.9)	6 (31.6)	
Blood levels, median (range)				
Hb, g/dl	9.0 (7.0–10.0)	9.1 (7.5–10.0)	8.5 (7.0–9.9)	**.002**
Leukocytes, $\times 10^9$/L	7.9 (1.7–75.5)	8.1 (1.7–75.5)	6.3 (2.7–25.5)	.48
Ferritin, ng/ml	180 (16–2889)	156 (16–2391)	496 (71–2889)	**.008**
EPO, U/L	48 (4–1742)	36 (4–688)	86 (21–1742)	**.034**
Ruxolitinib treatment (%)	59 (61.4)	48 (62.3)	11 (57.9)	.72
Transfusion dependency (%)	17 (17.7)	7 (9.1)	10 (52.6)	**<.0001**
Previous thrombotic events (%)	30 (31.2)	26 (33.8)	4 (21.0)	.43
Median time from diagnosis to B-ESA treatment, months (range)	13.0 (0–337)	12.9 (0–337)	14.0 (1.2–167)	.62
Duration of B-ESA treatment, months (range)	13.4 (1.4–107)	15.4 (1.4–107)	7.5 (2.3–103.8)	.87

Abbreviations: B-ESA, biosimilar erythropoiesis-stimulating agent; DIPSS, Dynamic International Prognostic Score System; EPO, erythropoietin; Hb, hemoglobin; MF, myelofibrosis.



	UNIVARIATE		MULTIVARIATE	
	HR (95% CI)	p	HR (95% CI)	p
Male sex	0.87 (0.56 - 1.37)	0.554		
Age ≤ 70 years	0.91 (0.56 - 1.47)	0.686		
JAK2 positivity	1.49 (0.92 - 2.41)	0.105		
Post-PV/ET MF	1.13 (0.72 - 1.79)	0.585		
DIPSS HIGH	0.69 (0.38 - 1.25)	0.217		
Time Dx - B-ESA > 6 months	0.96 (0.61 - 1.51)	0.876		
B-ESA alpha type	1.64 (1.02 - 2.62)	**0.041**	1.35 (0.84 - 2.17)	0.214
Transfusion independency	3.61 (1.66 - 7.85)	**0.001**	3.01 (1.37 - 6.60)	**0.006**
Hb > 8.5 g/dL	1.68 (0.91 - 3.11)	0.099		
Ferritin < 200 ng/mL	2.14 (1.37 - 3.35)	**0.001**	1.83 (1.17 - 2.87)	**0.009**
EPO < 50 U/L	1.58 (0.99 - 2.52)	0.060		

FIGURE 2 Univariate and multivariate exponential regression models on the rate (hazard) of response (24 months) to identify predictive factors of anemia response (AR) at baseline. B-ESA, erythropoiesis-stimulating agent; DIPSS, Dynamic International Prognostic Score System; Dx, diagnosis; EPO, erythropoietin; ET, essential thrombocythemia; Hb, hemoglobin; MF, myelofibrosis; PV, polycythemia vera.

the Hb level during the first 12 weeks of treatment; all of them were able to attain AR later on.

According to ruxolitinib treatment, similar AR rates (67% vs. 84% vs. 86%, $p = .31$) were observed in the 12/59 (20.3%) patients who started B-ESA before being on ruxolitinib compared with 25 patients (42.4%) who started B-ESA at the same time or within 3 months of ruxolitinib initiation (median time for ruxolitinib-induced anemia resolution) and 22 patients (37.3%) who started B-ESA after at least 3 months of JAK2 inhibitor.

The median duration of AR was 12.1 months (IR 1–101). Eleven patients (11%) lost AR after a median of 13.8 months (IR 4.1–40.2).

In multivariate analysis, only ferritin levels < 200 ng/ml (HR: 1.83, 95% CI: 1.17–2.87, $p = .01$) and transfusion independency (HR: 3.01, 95% CI: 1.37–6.60, $p = .006$) at baseline remained significantly associated with the achievement of AR (Figure 2).

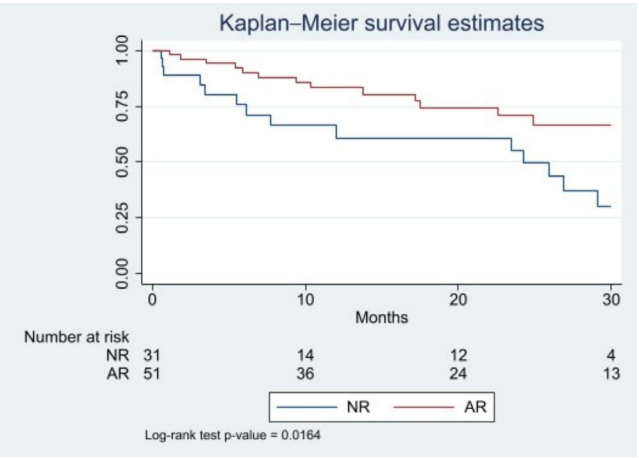


FIGURE 3 Estimate of the survival probability over time by response status. AR, anemia response—responder patients; NR, non-responder patients.

3.3 | Safety

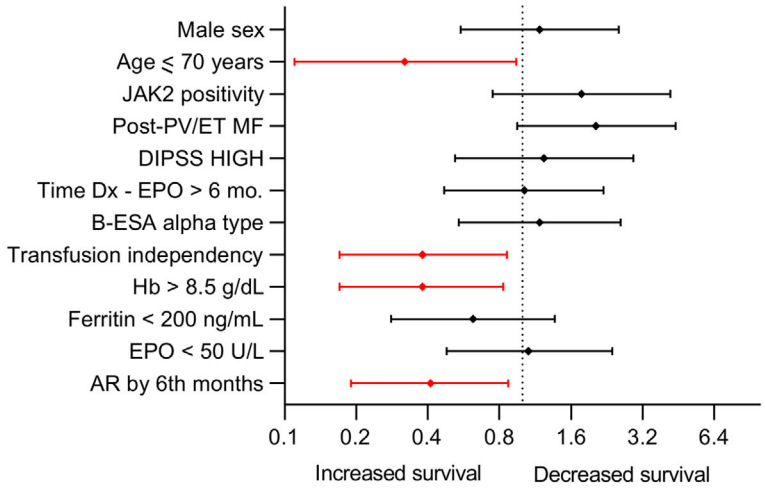
Overall, 30 patients (31%) required B-ESA dose reduction for too high Hb values (>12 g/dl). Only two patients (2%) discontinued treatment due to AEs, specifically one for pulmonary embolism and one for intolerance (vagal reaction). None of these events occurred in patients receiving ruxolitinib. No cases of increase in spleen size during B-ESA treatment were observed in ruxolitinib-responsive patients.

3.4 | Outcome

After a median follow-up of 43.8 months (IR 3.7–338) from diagnosis and 17.9 months (IR 1.4–107) from baseline, 48 patients (50%) had discontinued B-ESA treatment due to Hb level above 14 g/dl ($n = 2$), inadequate AR ($n = 9$) or loss of AR ($n = 6$), AEs ($n = 2$), ASCT ($n = 5$), death ($n = 21$), or lost follow-up ($n = 3$).

At the data cutoff of December 31, 2021, 38 patients (39%) had died, 11 of whom (28.9%) from leukemic evolution.

In univariate analysis, we observed a significant survival advantage from baseline for patients who responded to B-ESA, as reported in Figure 3 (24-month survival: 70.8% in AR vs. 55.3% NR group, $p = .016$). Other variables associated with improved outcome were age ≤70 years ($p = .037$), Hb > 8.5 g/dl ($p = .016$), and transfusion independency ($p = .019$) at baseline as shown in Figure 4. Among them, only age ≤ 70 years (HR: 3.44, 95% CI: 1.14–10.38, $p = .029$) and Hb > 8.5 g/dl (HR: 0.41, 95% CI: 0.17–0.99, $p = .047$) remained significantly associated with improved survival in multivariable



	UNIVARIATE		MULTIVARIATE	
	HR (95% CI)	p	HR (95% CI)	p
Male sex	1.18 (0.55 - 2.54)	0.678		
Age ≤ 70 years	0.32 (0.11 - 0.94)	**0.037**	0.29 (0.10 - 0.88)	**0.029**
JAK2 positivity	1.77 (0.75 - 4.19)	0.193		
Post-PV/ET MF	2.04 (0.95 - 4.41)	0.068		
DIPSS HIGH	1.23 (0.52 - 2.93)	0.634		
Time Dx - EPO > 6 mo.	1.02 (0.47 - 2.19)	0.967		
B-ESA alpha type	1.18 (0.54 - 2.59)	0.681		
Transfusion independency	0.38 (0.17 - 0.86)	**0.019**	0.74 (0.31 - 1.80)	0.507
Hb > 8.5 g/dL	0.38 (0.17 - 0.83)	**0.016**	0.41 (0.17 - 0.99)	**0.047**
Ferritin < 200 ng/mL	0.62 (0.28 - 1.37)	0.236		
EPO < 50 U/L	1.06 (0.48 - 2.38)	0.879		
AR by 6th months	0.41 (0.19 - 0.87)	**0.020**	0.48 (0.22 - 1.05)	0.067

FIGURE 4 Univariate and multivariate Cox model on the probability of survival after the 6-month landmark. AR, anemia response; B-ESA, erythropoiesis-stimulating agent; DIPSS, Dynamic International Prognostic Score System; Dx, diagnosis; EPO, erythropoietin; ET, essential thrombocythemia; Hb, hemoglobin; MF, myelofibrosis; PV, polycythemia vera.

analysis. Instead, achieving an AR at any time presented a trend for longer survival (HR: 0.48, 95% CI: 0.22–1.05 $p = .06$, Figure 4).

Of note, according to different cytoreductive treatments received, we did not observe a different outcome after B-ESA start among the patients exposed to ruxolitinib compared with those who received conventional therapy (principally hydroxyurea), with a median survival from baseline of 17.9 versus 19.9 months, respectively ($p = .274$).

4 | DISCUSSION

MF is a myeloproliferative neoplasm frequently characterized by anemia presenting at diagnosis or later during the disease course, and anemia is recognized as an adverse prognostic factor for survival.[3,16,17] Although ESA have an established role in managing anemia in several therapeutic settings, their role in MF is still largely undefined.

Previous experiences suggest that ESA have only limited activity in transfusion-dependent subjects with PMF, also increasing the risk of transformation to acute leukemia and exacerbating splenomegaly.[13] Other, and indeed most, recent retrospective studies suggested that both darbepoetin and epoetin alpha and beta could be effective for treating anemia in MF patients, and response rates ranging from 16% to 85% have been reported.[8–12] Such apparently divergent results may be related to heterogeneity between studies in study design concerning patient populations, response criteria, and assessment of treatment outcomes. Moreover, although baseline EPO levels and RBC transfusion requirements have been identified as having prognostic significance,[12] additional predictors of response to ESA in this setting can be expected to emerge as clinical experience grows. Indeed, although formal approval for the use of ESA in MF-related anemia is lacking, they are increasingly used in clinical practice as satisfactory treatment options for the management of anemia in MF patients are limited.[1,7]

B-ESA represent a low-cost alternative to originator erythropoietic agents in the treatment of chemotherapy-induced anemia in different oncology/hematology patients,[22] for example, in the setting of lymphoproliferative diseases and myelodysplastic syndromes (MDS).[23–25] In particular, evidence from studies in MDS showed that B-ESA were similar in terms of efficacy and safety to originator epoetin agents, as reported by a recent study in elderly MDS patients treated with B-ESA alpha[23] and a larger meta-analysis.[24] Recently, Vetro et al. reported the efficacy and safety data in the management of anemia within a prospective study of 36 patients with low-risk MDS who received B-ESA zeta at a dose of 40 000 U/week administered subcutaneously.[25] An erythroid response was achieved in 50% and 75% of patients, respectively, after 8 and 16 weeks of treatment, with five patients requiring a doubling of the weekly B-ESA dose to achieve AR. Nine AEs were reported, which in five patients (i.e., 14% of the study population) were grade 3–4, mainly represented by infections and worsening of existing hypertension.

Despite these encouraging results with B-ESA in the management of anemia in MDS, and although MDS and MF diseases share some key clinical and biological features, such as the onset in the elderly, the clonal nature, the chronic evolution, the potential progression to leukemic phase, and the prognostic role in both conditions of parameters, such as the level of endogenous EPO in eliciting an erythroid response, to date, no specific studies have been published on the use of B-ESA in the context of MF.

The present multicenter study reports, to our knowledge, the largest cohort of patients that received B-ESA for managing anemia in the MF setting. This study aims to broaden the mastery of the use of B-ESA in MF and to encourage a critical debate about the indications for using B-ESA in this real-life setting, analyzing 96 patients considered by their treating hematologist to be eligible for B-ESA.

Our preliminary data showed that B-ESA appears to be an effective and well-tolerated option for anemia treatment in the MF setting. First, we observed a large AR (80%), with 64 patients obtaining CR (67%). AR is quickly acquired (median time of 2.5 months) and maintained over time, as over 62% of patients (48/77) are still in response at 2 years. Transfusion independency at baseline and ferritin values <200 ng/ml seem to represent the stronger independent predictive factors for response to B-ESA, similar to previous studies with ESA originators.[8,9,12] This may suggest that early B-ESA treatment could lead to better AR in MF patients. Unlike these latter studies,[8,9] but similarly to the experience of Hernández-Boluda et al.,[12] the impact of low EPO levels at baseline is not remarkable. In this regard, it should be noted that our series is more contemporary, as 88.5% of patients started B-ESA treatment after 2015.

Accordingly, most patients in our study had baseline serum EPO levels considered to be inadequate for the degree of anemia by current clinical guidelines for hematological malignancies (median EPO at baseline 48.5 U/L).[3] This aspect may have had a favorable influence on the AR rate, which is significantly higher in our series than reported in some earlier studies.[8,13] However, our data reinforce the importance of including the measurement of baseline EPO levels in the therapeutic decision-making process for MF-related anemia.

Second, we analyzed the impact of concomitant B-ESA treatment in ruxolitinib patients on the achievement of AR and in terms of the efficacy of the JAK2 inhibitor. Anemia was reported in up to 83.8% of patients treated with ruxolitinib in the COMFORT studies.[10] As noted, the use of ESA was initially discouraged in the pivotal COMFORT-I clinical trial due to concerns that activation of the JAK pathway could potentially attenuate the activity of ruxolitinib in reducing spleen volume. Similarly, a corresponding reduction in the clinical efficacy of ESA could have been anticipated in the presence of JAK2 inhibition.[10] These concerns have not been substantiated in practice, perhaps at least in part because ESAs have a prolonged terminal half-life, whereas that of ruxolitinib is relatively short. Data from a post hoc analysis of the COMFORT-II study had already reported that a concomitant treatment with ESA in 13 of the 146 ruxolitinib-treated patients was well tolerated without adversely affecting the efficacy of ruxolitinib.[12] These findings were confirmed by a recent retrospective study in 59 patients with anemia receiving ruxolitinib treatment for MF, which found that the co-administration of ESA was well tolerated and effective in improving anemia, without any negative impact on the response to ruxolitinib.[9]

In the COMFORT studies, ruxolitinib-induced anemia resolved in the majority of patients within 12 weeks.[10] In our series, patients who received concomitant treatment with B-ESA and ruxolitinib at any time during the observation period had a similar response rate. In particular, a comparable AR rate was observed in the group of patients starting B-ESA more than 3 months after ruxolitinib (when ruxolitinib-induced anemia was likely resolved in most patients), compared to patients who started B-ESA within 3 months of ruxolitinib treatment. Therefore, these data confirmed that AR in the majority of cases was related to B-ESA treatment and not only to the spontaneous resolution of the early ruxolitinib toxicity on erythroid progenitors, similarly to the report of Crisà et al.[9]

Furthermore, B-ESA does not appear to negatively influence ruxolitinib efficacy because no cases of increase in spleen size during B-ESA treatment were observed in ruxolitinib-responsive patients.

Third, we observed negligible toxicity with B-ESA, with a discontinuation rate of 2%. An increased risk of thromboembolic events has been reported in patients with solid tumors receiving ESA, although the pathogenic mechanisms involved have not been clarified,[26] and the relationship between the maximum Hb level attained or the rate of Hb increase, and the rate of thrombosis remains to be defined.[27] In contrast, ESA are not associated with an increased risk of venous thrombosis in patients with MDS.[28] Although MF could be considered an inherent thrombophilic condition,[29] in our series, only a single thrombotic event occurred. Therefore, B-ESA is also safe in the setting of MF, similar to that in MDS.

Finally, our data also suggest a possible positive impact of AR on survival. Patients who achieved an AR at any time showed a longer survival trend, similar to other studies with originators ESA.[9,12] This observation, together with the significant correlation between Hb level >8.5 g/dl at baseline and improved survival, could suggest that early treatment with B-ESA before developing severe anemia and significant iron overload secondary to transfusion support could have a favorable impact on outcome.

The main limitation of this study is its retrospective nature. Indeed, selection bias, inadequate recognition of the degree and causality of AEs, and limitations due to possible additional unidentified parameters affecting survival cannot be avoided entirely. Nonetheless, the substantial number of included patients, several measures to reduce the risk of bias in evaluating the effects of B-ESA, based on the exclusion of all patients who had received any other concomitant drug with a potential impact on the erythroid improvement, together with the support of hematology centers with a particular focus on MF, and the accurate revision of each case history may compensate in part for any intrinsic shortcomings in our study. It should be noted that such limitations can hardly be circumvented in the case of a rare condition such as MF. Nevertheless, retrospective studies are at present an important source of data for personalized therapy.

In conclusion, B-ESA appears to be an effective and well-tolerated option for the treatment of anemia in the MF setting. We observe a great AR (80%) without significant toxicities, and the achievement of AR shows a trend for a potential survival benefit, as previously reported with originators ESA. Transfusion independency and ferritin levels <200 ng/ml at baseline are the strongest independent predictive factors for the achievement of AR. This may suggest that early B-ESA treatment should be a recommended option in managing anemia in the MF patient before transfusion dependency develops. Therefore, further prospective, controlled studies are required to confirm these findings and to evaluate the potential impact of AR on outcomes in a larger setting of MF patients.

AUTHOR CONTRIBUTIONS

All authors: Performed research, collected data, and reviewed and approved the final version of the article. **Elena Maria Elli and Elena Inzoli**: Designed the study, analyzed and interpreted data, performed the statistical analysis, and wrote the article. **Laura Antolini**: Analyzed and interpreted data and performed the statistical analysis. **Ivan Civettini**: Analyzed and interpreted data. **Laura Montelisciani**: Performed statistical analysis.

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CONFLICTS OF INTEREST

NP reports honoraria from Novartis. AC reports honoraria from Incyte and Novartis. EME reports honoraria from Novartis and AbbVie.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author.

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