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Received: 22 January 2023 | Revised: 28 April 2023 | Accepted: 30 April 2023

DOI: 10.1002/ajh.26960

CORRESPONDENCE

Real-world efficacy and safety of luspatercept and predictive factors of response in patients with lower risk myelodysplastic syndromes with ring sideroblasts

To the Editor:

Myelodysplastic syndromes (MDS) are myeloid malignancies predominating in the elderly, characterized by ineffective hematopoiesis and risk of progression to acute myeloid leukemia (AML).[1] In lower risk MDS, anemia is the pathological hallmark of the disease and a high proportion of patients eventually become dependent on red blood cell (RBC) transfusions. Transfusion-dependent anemia was found to be associated with reduced quality of life and shorter survival, mainly because of an increased risk of cardiovascular complications and death.

Erythropoiesis-stimulating agents (ESA) are the first-line treatment for anemia in MDS.[2] Limited options are available to treat transfusion-dependent anemia after ESA failure, and therefore most patients will continue to receive RBC transfusions only. Recently, a phase 3 randomized placebo-controlled trial[3] provided evidence for the efficacy of luspatercept in treating transfusion-dependent anemia in patients with lower risk MDS-RS who were refractory to ESA treatment. First results of real-world use of luspatercept were recently published.[4–6] Fondazione Italiana Sindromi Mielodisplastiche (FISiM) promoted a multicenter, observational trial to collect and analyze data on the efficacy and safety of luspatercept in a population of adult patients who were treated in a compassionate use program. This study was registered at ClinicalTrials.gov (NCT05520749). The Ethics Committees of all involved Hospitals approved the study.

Eligible patients were 18 years of age or older and had MDS-RS according to 2016 WHO criteria[7]; met criteria for IPSS-R very low, low, or intermediate risk[8]; were receiving regular RBC transfusions (i.e., ≥2 units/8 weeks during the 16 weeks before enrollment); and were refractory to or unlikely to respond to ESA therapy. Main exclusion criteria included prior treatment with hypomethylating agents or lenalidomide; an absolute neutrophil count $<0.5 \times 10^9$/L; and a platelet count $<50 \times 10^9$/L. Additional inclusion and exclusion criteria are listed in Table S1.

Luspatercept was administered according to label instructions. No restrictive transfusion policy was implemented, and treatment with an iron cheating agent was administered according to currently available guidelines.[2]

The statistical plan of the Medalist trial was replicated in our analysis to evaluate the effectiveness of luspatercept administration outside of a clinical trial. The primary endpoint was transfusion independence (TI) for ≥8 weeks during weeks 1–24. The main secondary endpoints were TI for ≥12 weeks, during weeks 1–24 and 1–48. All the outcome measures are reported in Appendix S1.

The efficacy analyses were performed in all enrolled patients who received at least one dose of luspatercept. A regression model was used to identify the optimal baseline transfusion burden thresholds for patients' stratification.

Overall, 215 patients were screened for enrollment in the Italian luspatercept compassionate use program, and 201 received at least one dose of the study drug between November 1, 2020, and January 30, 2022. Reasons for screening failure included disease, neutropenia, and thrombocytopenia. The cutoff date for patients' data collection was August 31, 2022. The median follow-up was 377 days (21–534).

Median age at enrollment was 74 years (31–89). At least one comorbidity requiring ongoing treatment was present in 134 (66.7%) patients, and at least three were present in 43 (21.4%). Baseline median transfusion burden was 7 units/8 weeks (2–22). The complete baseline characteristics of the patients are listed in Table S2.

Transfusion independence (TI) for ≥8 weeks in the first 24 weeks was achieved in 62 (30.8%) patients. The percentage of patients who met the primary outcome measure increased to 39.3% when the observation period included the first 48 weeks. Among patients who had a primary response ($n = 79$), 23 (29.1%) had multiple TI intervals lasting 8 weeks or longer, and 12 (15.2%) had at least three or more TI intervals.

A primary response was achieved at the starting dose level (1 mg/kg) in 33 (41.8%) subjects, while dose increases at 1.3 mg/kg and 1.75 mg/kg were performed in 24.1% and 34.1% of primary responders, respectively. The median longest duration of primary response was 23.9 weeks (8–70). At data cutoff, 34 patients were still in a TI interval (see Figures S1, S4 and S5).

An erythroid response according to IWG 2006[9] criteria was observed in 71 (35.3%) patients during the first 24 weeks of treatment. A mean increase in the hemoglobin level of 1.5 g/dL or more was observed in 28 (13.9%) and 44 (21.9%) patients in the first

TABLE 1 Evaluation of primary and secondary endpoints and erythroid response in the FISiM-luspatercept population stratified according to baseline transfusion burden.

	FISiM study ($n = 201$)	*p*-value
Primary endpoint		
RBC-TI ≥8 weeks during Weeks 1–24, *n* (%)	61 (30.3)	
Baseline transfusion requirements		
≤4 Units/8 weeks, *n* (%)	27 (51.9)	<.0001
5–7 Units/8 weeks, *n* (%)	19 (37.3)	
≥8 Units/8 weeks, *n* (%)	13 (16.7)	
TI duration, median, weeks	23.9	
Baseline transfusion requirements		
≤4 Units/8 weeks, median (IQR)	33.9 (18–49)	.0045
5–7 Units/8 weeks, median (IQR)	27.0 (11–41)	
≥8 Units/8 weeks, median (IQR)	13.9 (9–24)	
Secondary endpoints		
RBC-TI ≥8 weeks, weeks 1–48, *n* (%)	79 (39.3)	
Baseline transfusion requirements		
≤4 Units/8 weeks, *n* (%)	29 (55.8)	
5–7 Units/8 weeks, *n* (%)	22 (40.7)	<.0001
≥8 Units/8 weeks, *n* (%)	20 (25.6)	
RBC-TI ≥12 weeks, weeks 1–24, *n* (%)	38 (18.9)	
Baseline transfusion requirements		
≤4 Units/8 weeks, *n* (%)	16 (30.8)	
5–7 Units/8 weeks, *n* (%)	13 (24.1)	<.0001
≥8 Units/8 weeks, *n* (%)	7 (9.0)	
RBC-TI ≥ 12 weeks, weeks 1–48, *n* (%)	59 (29.4)	
Baseline transfusion requirements		
≤4 Units/8 weeks, *n* (%)	22 (42.3)	<.0001
5–7 Units/8 weeks, *n* (%)	18 (33.3)	
≥8 Units/8 weeks, *n* (%)	12 (15.4)	
Erythroid response		
Reduction of ≥70% in total RBC units transfused during Weeks 1–24		
Baseline transfusion requirements		
≤4 Units/8 weeks, *n* (%)	17 (32.1)	.1050
5–7 Units/8 weeks, *n* (%)	18 (31.6)	
≥8 Units/8 weeks, *n* (%)	17 (18.7)	
Dose at first RBC-TI ≥8 weeks, weeks 1–48, *n* (%)		
Baseline transfusion requirements		
≤4 Units/8 weeks, *n* (%)		
1.00 mg/kg	17/33 (51.5)	.0490
1.33 mg/kg	11/33 (33.3)	
1.75 mg/kg	5/33 (15.2)	
5–7 Units/8 weeks, *n* (%)		
1.00 mg/kg	7/19 (36.8)	
1.33 mg/kg	5/19 (26.3)	
1.75 mg/kg	7/19 (36.9)	
≥8 Units/8 weeks, *n* (%)		
1.00 mg/kg	7/27 (25.9)	
1.33 mg/kg	6/27 (22.2)	
1.75 mg/kg	14/27 (51.9)	

Note: *p*-values calculated with Fisher's exact test for categorical variables and ANOVA for continuous variables.
Abbreviation: RBC-TI, red blood cell transfusions independence.

24 and 48 weeks of treatment, respectively. Mean change in serum ferritin concentration was −518 μg/L (95%–801; −235) after the first 12 administrations of luspatercept (see Table S4). No correlation was found between the reduction in ferritin concentration and an increase in hemoglobin concentration.

During the first 24 weeks of treatment, 14 (6.9%) patients achieved a major erythroid response according to the IWG 2018 criteria. In the high transfusion burden subgroup, a minor erythroid response was observed in 76 (41.9%) patients (see Table S6). Additional data regarding trends in hemoglobin concentration, absolute neutrophil count and platelet count are provided in Figures S3, S6 and S7.

Multiple logistic regression analysis was performed to investigate the correlation between the probability of achieving a primary response and the baseline characteristics of the patients. A significant association was found between the baseline transfusion burden and the individual probability to achieve TI ($p < .001$). No correlation was observed with age, sex, IPSS-R risk, time since initial diagnosis, and time since first RBC transfusion.

We defined an optimal threshold for RBC transfusions with respect to the probability to achieve TI and, accordingly, we stratified our patient population in three subgroups: low (≤4 RBC units/8 weeks), intermediate (5–7 RBC units/8 weeks), and high transfusion burden (≥8 RBC units/8 weeks).

Such stratification identified groups with a different probability to achieve TI and different duration of TI, as shown in Table 1.

Median time on treatment was 294 days (21–526) and the median number of administered doses was 14 (2–25). At least one increase from the baseline recommended dose of 1 mg/kg occurred in 188 (93.5%) patients. Overall, 164 (81.6%) patients received the maximum allowed dose of 1.75 mg/kg at least once during the study period. The median dose of luspatercept at first TI response was 1.33 mg/kg. Although 41.8% [33 of 79] of patients who achieved TI had their first response at the starting dose (1.0 mg/kg), 58.2% had their first response after dose increases. The dose at first response was positively correlated with baseline transfusion burden.

During the study period, serious adverse events (SAE) occurred in 35 (17.4%) patients. The most frequently observed SAE were cardiac events (hypertension, acute heart failure, atrial fibrillation; $n = 11$), acute kidney injury ($n = 1$), infections ($n = 10$), COVID-19 pneumonia ($n = 4$), and falls leading to bone fractures ($n = 4$). Overall, 20 patients died during the study period. Grade 4 thrombocytopenia and neutropenia, according to the CTCAE v5, were observed in 1 and 8 patients, respectively. All were recorded in patients who showed low counts at baseline and were not correlated with disease progression or evolution.

Evolution to AML occurred in 5 (2.5%) patients (see Figure S2). All patients who showed evolution to AML were still being treated with luspatercept at the time of progression. Treatment discontinuation occurred in 87 (43.3%) patients. The main reasons for treatment discontinuation were lack of benefit or loss of response (64.4%), death (14.9%), and consent withdrawal (4.6%). Additional information regarding treatment exposure and treatment safety are provided in Tables S5 and S7.

Results of randomized clinical trials (RCTs) represent the basis for approving drugs or interventions for clinical use.[10] However, RCTs require subjects' selection that prevents participation of some patients to the study. Moreover, patients in RCT receive the intervention in highly controlled settings unlike those in clinical practice. Additionally, compliance in RCT far exceeds that observed outside of clinical trials. All these factors may generate gaps between evidence from RCT and real-world data, which could be particularly critical when interventions are complex, costly, and, as in case of MDS, involve older individuals with physical and cognitive frailty.

In this study, we were able to confirm that luspatercept was effective for treating transfusion-dependent anemia outside the setting of a clinical trial and we observed that the benefit extended beyond the achievement of TI, producing a significant reduction in the number of transfusions. Importantly, baseline transfusion burden can identify subgroups of patients with distinct probability to have a clinical benefit from the treatment.

As expected, our real-world MDS-RS population included subjects who were older when compared with the Medalist cohort and was enriched in significant concomitant comorbidities. Overall, we were faced with frail patients with potentially reduced treatment compliance, and in which the presence of comorbidity may concur to increase the severity of anemia. Despite that, we observed a response rate that was comparable to that of the Medalist study (see Table S3 for a direct comparison) and higher than what was previously reported in a real-world setting.[4] We also observed a high compliance rate and a manageable tolerability profile. The incidence of AML was low and consistent with the natural history of MDS-RS.[11–13]

Since only a proportion of patients achieve TI with luspatercept treatment, the identification of predictive factors associated with individual probability to achieve is of immediate clinical utility and could optimize patient management. Predictors of response previously published in other studies[4,5] were not found to be significant in our analysis, which included a larger and more homogeneous cohort of MDS-RS patients. In our observations, patients with higher transfusion burden had a lower probability to obtain a clinical benefit from luspatercept. An accurate evaluation of patients' baseline characteristics is deemed mandatory to maximize the clinical benefit of luspatercept administration.

These findings may reinforce the hypothesis that luspatercept could be more effective in early disease phases when ineffective erythropoiesis represents a major driver of MDS-related anemia.

Overall, the results of the present study could be useful for both improving clinical management of patients and optimizing healthcare policies in MDS-RS with transfusion-dependent anemia.

FUNDING INFORMATION

European Union – Horizon 2020 program (GenoMed4All project #101017549 to M.G.D.P.; Transcan_7_Horizon 2020 – EuroMDS project #20180424 to M.G.D.P.); AIRC Foundation (Associazione Italiana per la Ricerca contro il Cancro, Milan Italy – Project #22053 to M.G.D.P.); PRIN 2017 (Ministry of University & Research, Italy – Project 2017WXR7ZT to M.G.D.P.); Ricerca Finalizzata 2016 and 2018 (Italian Ministry of Health, Italy – Project RF2016-02364918 to M.G.D.P. and Project NET-2018-12 365 935 to M.G.D.P.); Beat Leukemia Foundation, Milan Italy (to M.G.D.P.).

CONFLICT OF INTEREST STATEMENT

Pellegrino Musto: Honoraria: Bristol Meyers Squibb, Celgene; Esther Natalie Oliva: Advisory Boards: Alexion, Bristol-Meyers-Squibb, Celgene, Daiichi-Sankyo, Novartis, Janssen; Consultancy: Alexion, Bristol-Meyers-Squibb, Daiichi Sankyo; Claudio Fozza: Research Support: Bristol-Meyers-Squibb, Celgene; Valeria Santini: Consultancy: Bristol Myers Squibb, Novartis; Participation on a Data Safety Monitoring Board or Advisory Board: Astex, Bristol Myers Squibb, Geron, Gilead, Menarini, and Novartis. The rest of the authors declare no competing interests.

DATA AVAILABILITY STATEMENT

Requests for access to data from the study should be addressed to FISiM scientific committee (please contact Matteo G Della Porta at matteo.della_porta@hunimed.eu). All proposals requesting data access will need to specify how the data will be used, and all proposals will need the approval of the FISiM scientific committee before data release.

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A preliminary analysis of the study was presented at the 2022 ASH Annual Meeting in New Orleans.

This study was registered at ClinicalTrials.gov (NCT05520749). The Ethics Committees of all involved Hospitals approved the study.

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SUPPORTING INFORMATION

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