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CASE REPORT

Luspatercept in combination with recombinant erythropoietin in patients with myelodysplastic syndrome with ring sideroblasts: Stimulating early and late-stage erythropoiesis

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Abstract

Patients with myelodysplastic syndromes and ring sideroblasts (MDS RS) are clinically characterized by severe anemia and transfusion need. Erythropoiesis-stimulating agents (ESAs), which stimulate hemoglobin production and early maturation of erythroid precursors, are effective only in a portion of patients and for limited time. Luspatercept, an inhibitor of the TGF-beta pathway, is beneficial in unblocking late-stage erythropoiesis and has been approved for MDS RS patients failing or not-candidate to ESAs. ESAs and/or luspatercept failure represents an unmet clinical need and most patients become life-long transfusion dependent. Here, we describe the clinical combination of luspatercept with ESAs (subcutaneous epoetin alpha 40–80 000 IU/week) in seven MDS RS patients. Two patients had ESAs as pre-existing therapy, while five were re-challenged with ESAs as add-on treatment due to luspatercept failure. Three patients achieved hematologic improvement, and one became transfusion independent. No adverse events were noted. This is the first clinical evidence that stimulating both early and late-stage erythropoiesis may offer a further option for this challenging patient population.

KEYWORDS
low-risk myelodysplastic syndromes, luspatercept, recombinant erythropoietin, ring sideroblasts, SF3B1

Novelty statements

- This is the first report of clinical combination of luspatercept with erythropoiesis-stimulating agents (ESAs).
- Luspatercept combined with ESAs (epoetin alpha 40–80 000 IU/week) was safe, induced hematologic improvement in 3/7 patients and transfusion independence in one.
- The addition of ESAs to luspatercept may be considered in patients not responding or losing response to luspatercept, who have permissive endogenous erythropoietin levels.

1 | INTRODUCTION

Myelodysplastic syndrome with ring sideroblasts (MDS RS) is a low-risk MDS characterized by ineffective erythropoiesis and consequent peripheral cytopenias, especially anemia. The latter is generally severe and poorly responsive to erythropoiesis-stimulating agents (ESAs), with consequent high transfusion burden.[1] Molecularly, the disease is marked by the presence of SF3B1 mutation in >80% of cases, leading to the definition of MDS-SF3B1 as a distinct entity in the most recent WHO and ICC classification.[1,2] Luspatercept, a TGF-beta-pathway inhibitor, showed high clinical activity in MDS RS patients and was recently approved for the treatment of anemia in patients failing or not candidate to ESAs.[3,4] Since luspatercept acts by re-activating late-stage erythropoiesis and ESAs mainly act on early stage erythropoiesis, we hypothesized a possible role of combination therapy in treating anemia in MDS RS patients.

2 | MATERIALS AND METHODS

All patients with MDS RS treated with luspatercept in combination with ESAs at two tertiary hematologic centers in Milan, Italy were retrospectively evaluated. All patients also fit the newest WHO classification for MDS-SF3B1 or MDS-RS.[1,2] Luspatercept was administered subcutaneously according to current data sheet (1–1.75 mg/kg every 3 weeks). Endogenous (e)EPO was evaluated before ESAs start, and patients with values <200 IU/L received subcutaneous epoetin alpha 40 000 U/week, while those with higher values received 80 000 U/week. Hematologic data and number of RBC transfusions were collected at each cycle of luspatercept, and hematologic improvement (HI) was assessed according to the revised International Working Group (IWG) 2018 criteria.[5] The study was conducted according to Helsinki Declaration, off-label use of ESAs was approved at the local center according to national law, and patients gave informed consent.

3 | CASE SERIES

Seven patients were included, all elderly males, with a median age of 83 years (range 70–90). All patients were high transfusion burden (>8 RBCU/16 weeks). Myeloid gene panel by NGS showed SF3B1 mutation in 6/7 patients, with a median VAF of 36.35%; two patients

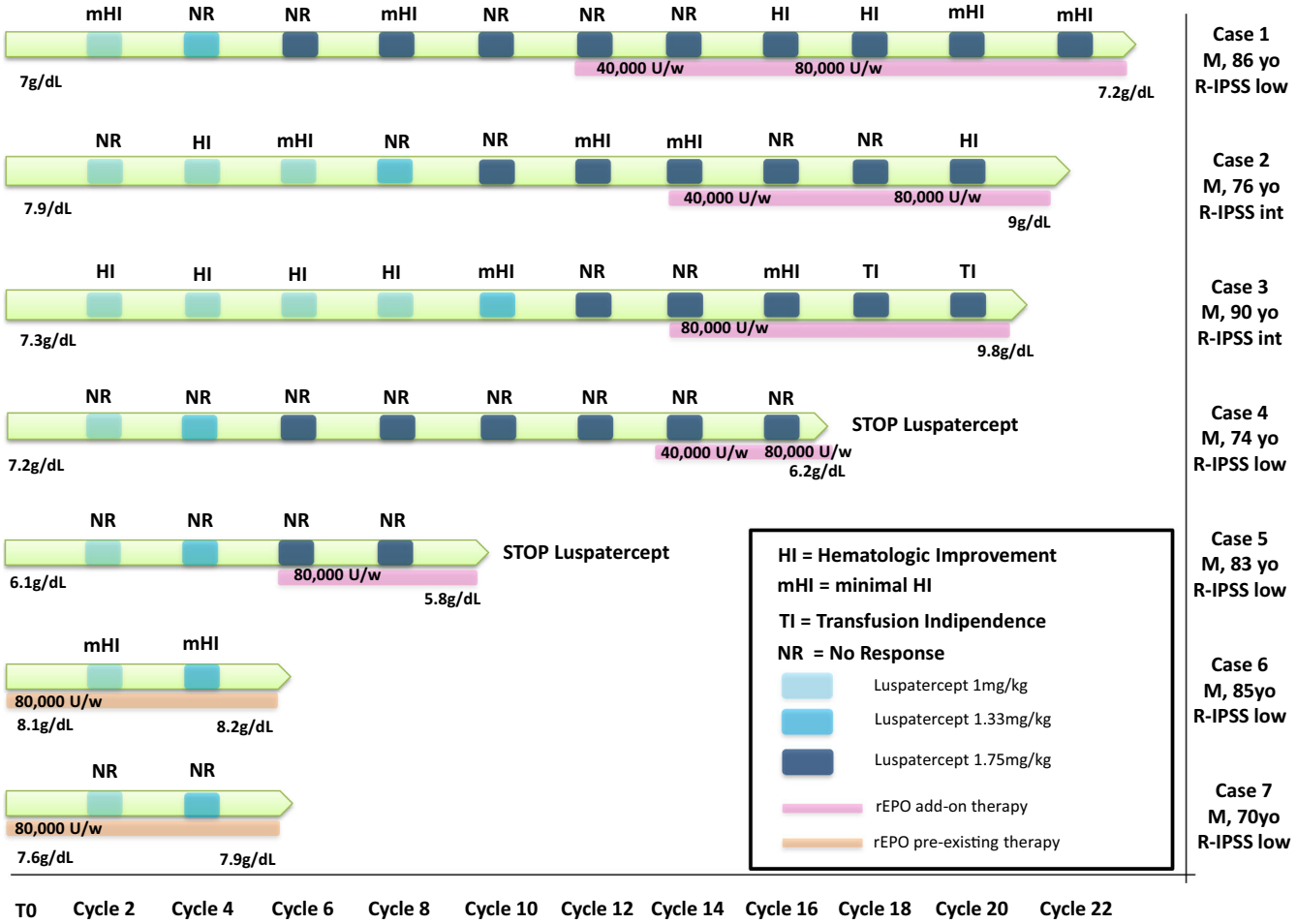

FIGURE 1 Luspatercept and recombinant erythropoietin (ESA) treatment in patients with myelodysplastic syndromes with ring sideroblasts. Boxes with different shades of blue represent luspatercept doses; pink bars represent ESA therapy; Hb value at last follow-up is reported for each patient. ESA, erythropoiesis-stimulating agent; HI, hematologic improvement; mHI, minimal hematologic improvement.

showed comutations including TET2 and ASXL1 in one patient and SH2B3 in the other. The patient that did not harbor SF3B1 mutation showed >50% RS at morphological analysis and harbored TET 2 and SRSF2 mutations.

According to the revised version of the international prognostic scoring system (IPSS-R), three patients were classified as intermediate risk, while the others were lower risk. At the time of luspatercept start, all patients had failed ESAs and median Hb values were 7.3 g/dL (6.1–9.9). Median neutrophil counts were $3.1 \times 10^3/mm^3$ (0.8–4.9) and platelets $200 \times 10^3/mm^3$ (43–282). The median number of RBC units transfused in the previous 8 weeks before luspatercept initiation was 8 (3–11). Figure 1 shows the timing and doses of luspatercept and ESAs treatment. Two patients had received ESAs as pre-existing therapy (both at 80 000 U/week), while five patients were re-challenged with ESAs as add-on treatment due to non or loss of response to luspatercept. The median eEPO value in these latter subjects was 250 (99–445) IU/L, and three patients initially received epoetin alpha 40 000 U/week and then escalated to 80 000 U/week due to non-response. Overall, three patients (Cases 1–3) achieved HI, and one of them became transfusion independent. In the two patients who had pre-existing ESA treatment, luspatercept follow-up has not reached 24 weeks yet, and response evaluation was based on the first 18 weeks of treatment. Table S1 details pre-transfusion Hb and transfusion need for each patient at each luspatercept cycle. Specifically, Case 1 achieved minimal HI (mild Hb increase) with luspatercept after cycles 2 and 6, and lost response thereafter; ESA was added at cycle 12 with HI (reduction of transfusion burden) after three further cycles. Case 2 initially reached HI (Hb increase with reduced transfusion requirement) after cycle 4 but showed several oscillations of pre-transfusion Hb (7–9 g/dL). At cycle 13, ESA was added obtaining HI (transfusion independence) after further six cycles. Case 3 achieved HI (transfusion independence) after two cycles of luspatercept but lost response after cycle 10; ESA was added at cycle 14 and he became transfusion independent. Case 6 had ESA as a pre-existing therapy and experienced a minimal HI (mild Hb increase) after luspatercept start. The other cases (Cases 4, 5, and 7) did not respond to luspatercept, nor to combination with ESAs (the latter added at cycle 14 in Case 4 and cycle 7 in Case 5, and was already ongoing at luspatercept start in Case 7). Luspatercept treatment is still ongoing in all patients except for Cases 4 and 5, who stopped due to non-response; regarding Case 7, who did not achieve response after 4 cycles, we intend to reach 12 cycles of luspatercept and suspend treatment if no response is achieved. Finally, no treatment emerging adverse events were registered with the combination therapy.

4 | DISCUSSION

Here, we report for the first time the clinical combination of luspatercept and ESA in MDS RS patients and show a benefit in about half of cases. Importantly, this combination appeared safe as no treatment-related adverse events were observed.

Despite the limited number of patients, the availability of detailed clinical data and the close follow-up represent an added value to this case series. The two treatments used as single agents have favorable outcomes: luspatercept induced transfusion independence in 38% of cases in the pivotal study[4] and ESA was reported effective in 58% of patients in historical series.[6] We speculated a possible synergistic effect of the two treatments in MDS RS patients as they act on different stages of erythropoiesis. It has been reported that in MDS, clonal features along with the pro-inflammatory bone marrow microenvironment impair erythroid differentiation in both the early and terminal stages. Moreover, TGF-beta pathway upregulation blocks proliferation and induces apoptosis of erythroblasts thus affecting late-stage differentiation. Luspatercept, by inhibiting TGF-beta receptor signaling, may revert this pathogenic mechanism.[3,4,7] On the other hand, ESAs act on early stage erythropoiesis by inhibiting apoptosis and promoting erythroid progenitor survival. Thus, a combination therapy may result in the simultaneous stimulation of different phases of the erythropoiesis, consistently with the synergistic effect observed in a preclinical murine model.[8] Interestingly, another recent report[9] evaluated this combination in 28 MDS patients and showed a clinical benefit in about 1/3 of patients. Predictors of response included prior response to luspatercept, frontline combination, endogenous EPO < 500 U/L (as in all of our cases), and presence of SF3B1 mutation (positive in 6/7 in our series).

Another example of concomitant use of hematopoiesis stimulating agents is the combination of ESAs with granulocyte-colony stimulating factor (G-CSF) in MDS patients failing ESA alone. In the real world, the management of patients failing ESAs and/or luspatercept represents an unmet clinical need. An attempt with a different ESA agent has been reported effective in up to 40% of cases, and intermittent responses have been lately documented on long-term treatment with luspatercept.[5] Here, we show that retreatment with ESA along with luspatercept may represent a further therapeutic option, provided permissive eEPO levels. This combination is feasible and beneficial in about half of MDS RS subjects by acting on early and late-stage erythropoiesis.

AUTHOR CONTRIBUTIONS

Bruno Fattizzo, Francesco Versino, Marta Bortolotti, Lorenzo Rizzo, Marta Riva, and Wilma Barcellini followed patients, collected data, wrote the article, and revised it for important intellectual content.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data are available within the manuscript and further may be available upon reasonable request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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