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637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Efficacy and Safety of Luspatercept +/- Erythropoiesis-Stimulating Agent (ESA) in Patients with Myelodysplastic Syndromes with Ring Sideroblasts (MDS-RS): A French Multicenter Prospective Real-Life Registry

Thibault Comont[1], Maud D'Aveni[2], Laurence Schenone[3], Jose Miguel Torregrosa-Díaz[4], Lorea Aguinaga, MD[5], Juan Pardo[6], Marie Sebert, MD PhD[7], Sorin Visanica[8], Clemence Santana[9], Lenaig Le Clech[10], Aspasia Stamatoullas, MD[11], Sylvain Thepot, MD[12], Etienne Daguindau[13], Guillaume Beziat[14], Teresa Botin[15], Sophie Dimicoli[16], Sophie Park, MD PhD[17], Etienne Paubelle[18], Bohrane Slama[19], Lise Willems[20], Houria Debarri[21], Emmanuel Gyan[22], Claire Calmettes[23], Odile Rauzy[1], Fatiha Chermat[24], Michaela Fontenay, MD PhD[25], Lionel Ades, MDPhD[26], Pierre Fenaux[27]

[1] Toulouse University Hospital, Toulouse, France
[2] Department of Hematology, Centre Hospitalier Régional Universitaire (CHRU), Vandoeuvre-les-Nancy, France
[3] CHRU De Nancy, Vandoeuvre-lès-Nancy, FRA
[4] Poitier University Hospital, Poitiers, FRA
[5] Saint Louis Hospital AP-HP, Paris, France
[6] Saint louis Hospital APHP, Paris, France
[7] Hôpital Saint-Louis, Paris, France
[8] CH METZ, Metz, FRA
[9] Centre Léon Bérard, LYON CEDEX 08, FRA
[10] CH Lorient, Quimper, FRA
[11] Centre Henri Becquerel, Rouen, France, Rouen, FRA
[12] Department of Clinical Hematology, Angers University Hospital, ANGERS, France
[13] Department of Clinical Hematology, CHU de Besançon, Besançon, France
[14] Albi Hopital, Albi, France
[15] Castres Hospital, CASTRES CEDEX, FRA
[16] Bordeaux University Hospital, Pessac, FRA
[17] CHU Grenoble, Grenoble Cedex 9, FRA
[18] Hospices Civils de Lyon, Lyon, FRA
[19] Service d'onco-hématologie, Centre Hospitalier Général d'Avignon, Avignon, FRA
[20] Hôpital Cochin, AP-HP, Paris, France
[21] CHR Metz-Thionville, Ars Laquenexy, FRA
[22] Service D'Hematologie Et Therapie Cellulaire, Tours Cedex, France
[23] CH de Périgueux, Périgueux, France
[24] Saint Louis Hospital, Paris, France
[25] HOPITAL COCHIN, Paris, FRA
[26] Hôpital Saint-Louis, Hematology Department, Hopital Saint Louis, Paris, France
[27] Hopital Saint Louis, Groupe Francophone des Myelodysplasies, Paris, France, PARIS, FRA

Background

EMA has recently approved Luspatercept (LUSPA) for the treatment of anemia in adult patients with RBC transfusion-dependent (TD) very low- to intermediate- risk MDS-RS or MDS/MPN with ringed sideroblasts and thrombocytosis (MDS/MPN-RS-T) having failed an ESA. We designed a French observational registry of patients treated with LUSPA according to this label. In case of primary/secondary failure to LUSPA, we also investigated the effect of adding an ESA to LUSPA. The basis of this combination followed a GFM trial showing that, in non-del 5q lower risk MDS failing an ESA, Lenalidomide + ESA gave better results than Lenalidomide alone (Toma A et al. Leukemia. 2016 Apr;30(4):897-905). In a phase I study (GFM Combola trial), we found no unexpected side effects in the LUSPA -ESA combination (unpublished).

Patients and treatment

This French multicenter prospective observational registry started when the drug became available (July 2022), with a starting dose of 1 mg/kg SC every 3 weeks (2 infusions) and, in the absence of erythroid response increase to 1.33mg/kg (2 injections) and to 1.75 mg/kg (3 injections). In the absence of response after those 7 infusions, the addition of ESA (30 KU /week during 1 month and, if no response, 60 KU/week during 3 months) was recommended.

Results

Between July 2022 and January 2023, 108 patients (median age 70 years, 47% males) were included. Median time from diagnosis to LUSPA treatment was 64 months (IQR 40-99). According to WHO 2016, 86% of the patients had MDS-RS, 9% MDS-RS-T, and 5% MDS-EB1 or MDS-MLD (but with > 15% ringed cells and/or *SF3B1* mutation). IPSS-R was very low, low, int in 96%, and high in 4%, IPSS-M very low/low/moderate low in 82%. Sixty-six of the 73 (90%) patients tested molecularly had *SF3B1* mutation. All patients had received an ESA and 44 (41%) other treatments (1 to 6, median 1). The median duration of LUSPA exposure was 6.5 months (range 0.5-11), and 94% of patients had received at least 2 months of treatment. Erythroid response (HI-E, according to IWG 2018 criteria) to LUSPA alone was currently evaluable in 83 patients; 76 of them were RBC-TD before LUSPA (23 low TB (LTB) (1-5 units /8 weeks) and 53 high TB (HTB) (≥ 6 units /8 weeks)), and 30 (39%) of these achieved RBC-TI with no relapse after a median of 6.5 months (range 4.4-11). All 9 non-TD patients obtained HI-E and were still responders after a median of 8 (range 6.5-9) months. Of the 85 patients evaluable for response to LUSPA alone, 34% and 48% required a dose increase once or twice, respectively. The prognostic value of IPSS-R karyotype, IPSS-R, number of somatic mutations, LTB, HTB, number of treatments before LUSPA, previous lenalidomide exposure, and iron chelation was analyzed for their prognostic value on HI-E. In multivariate analysis, HTB was the only variable statistically associated with lower HI-E (OR 0.19 [95%CI: 0.03-0.91, p=0.047] independently of IPSS-R and number of somatic mutations.

At least 1 adverse event (AE) was seen in 38/103(37%) of the patients who received at least 2 doses of LUSPA, and 12 patients presented at least one severe AE (grade 3-4 according to CTCAE 5.0): including dizziness (in 5 patients), asthenia (n=4), peripheral and axial arthralgia (n= 4), headache (n=2), described by the patients as different from those they experienced with anemia. With a median follow-up of 6 months (IQR 5-8), 20 patients (18.5%) had discontinued LUSPA before 6 months of exposure due to severe AE (n=8, 7.4%, asthenia, arthralgia, dizziness, headache), lack of HI-E (n=3), disease progression (n=3), infection (n=3), death from intercurrent disease (n=2), acute coronary syndrome (n=1).

After LUSPA failure, 26 patients (24.1%) received a combination of LUSPA and ESA and are currently followed. Efficacy and safety will be presented at the meeting.

We also tried to correlate gene expression and GDF-11 levels with response. Results will be available at the meeting.

Conclusions

In this real-life study, we confirmed the results of LUSPA in MDS-RS reported in the MEDALIST study. We observed a significant number of adverse events attributed to LUSPA, some of which led to treatment discontinuation. The importance of RBC transfusion burden was the only prognostic factor of erythroid response.

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