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Luspatercept for the treatment of anemia in myelodysplastic syndromes and primary myelofibrosis

Pierre Fenaux,[1,2] Jean Jacques Kiladjian,[2,3] and Uwe Platzbecker[4,5]

[1]Service Hématologie Séniors, Hôpital St Louis, Assistance Publique–Hôpitaux de Paris, Paris, France; [2]Department of Hematology, Université Paris Diderot, Paris, France; [3]Centre d'Investigations Cliniques, Assistance Publique–Hôpitaux de Paris, Paris, France; and [4]Medical Clinic and [5]Policlinic 1, Hematology and Cellular Therapy, Leipzig University Hospital, Leipzig, Germany

Anemia of lower-risk myelodysplastic syndromes (MDSs) and primary myelofibrosis (PMF) generally becomes resistant to available treatments, leading to red blood cell (RBC) transfusions, iron overload, shortened survival, and poor quality of life. The transforming growth factor-β superfamily, including activins and growth differentiation factors (GDFs), is aberrantly expressed in lower-risk MDSs and PMF. Luspatercept (and sotatercept), ligand traps that particularly inhibit GDF11, lead to RBC transfusion independence in 10% to 50% of lower-risk MDSs resistant to available treatments, and have started to be used in PMF. (*Blood*. 2019;133(8):790-794)

Introduction: the burden of anemia in lower-risk MDSs

Until recently, lower-risk myelodysplastic syndrome (MDS) was defined by a low or intermediate 1 score in the classical International Prognostic Scoring System (IPSS). These patients were thought to have low risk of acute myeloid leukemia (AML) progression, relatively prolonged survival, but a high prevalence of anemia, resulting from ineffective hematopoiesis and accounting for most clinical symptoms.[1] Improvements with prognostication came with the revised IPSS that modified the impact of the various IPSS variables (ie, cytopenias, marrow blast percentage, and cytogenetics)[2] and the assessment of somatic mutation(s) (most being unfavorable, especially if occurring in combination). These parameters identified 25% of lower-risk patients having a worse prognosis than implied by the original IPSS. Still, 75% of IPSS lower-risk MDSs have limited risk of AML progression, especially MDS with ringed sideroblasts (MDS-RS in the World Health Organization [WHO] 2016 classification) with SF3B1 mutation (present in 90% of MDS-RS).[3]

Anemia of lower-risk MDS can be treated symptomatically by red blood cell (RBC) transfusions or by treatments aimed at increasing the hemoglobin (Hb) level and preventing transfusions.[4] Patients receiving RBC transfusions, however, generally have chronic anemia with average Hb < 9 g/dL, associated with fatigue, lower quality of life, excess morbidity and cardiovascular mortality, and transfusion iron overload.[4-6] RBC transfusions also mobilize large resources, and their average annual cost is 10 to 15 000 euros (not including iron chelation).[4] Thus, drug treatment potentially avoiding RBC transfusions is generally sought.

Drug treatment of anemia in lower-risk MDSs

Recombinant erythropoietin (EPO) and glycosylated forms (darbepoetin) are generally the first-line treatment of anemia of lower-risk MDSs, except in MDS with isolated del 5q, where lenalidomide yields better erythroid response (hematological improvement-erythroid [HI-E]) rates.[7-12] Erythroid response to EPO and darbepoetin, (defined by a >1.5 g/dL increase in Hb in transfusion-independent [TI] patients and significant reduction or disappearance of transfusion need in transfusion-dependent [TD] patients) is observed in 30% to 60% of patients, with a median response duration of 18 to 24 months.[7-11] We and others found that, in lower-risk MDSs, EPO and darbepoetin had no impact on AML progression but were associated with improved survival, strongly supporting that this treatment and/or maintaining an adequate Hb level and/or avoiding iron overload can reduce nonleukemic deaths in lower-risk MDSs.[11,13]

Better response to EPO and darbepoetin is seen in patients with low baseline EPO levels (<200 U/L), low (<2 RBC units per month) or absent RBC transfusion requirement, normal cytogenetics, marrow blasts <5%, and possibly fewer somatic mutations.[7,10,11,14] In 2 large series, we found MDS-RS to have similar response rates but shorter responses to EPO and darbepoetin than other lower-risk MDSs.[10,15]

Current treatment of anemia after EPO or darbepoetin failure

In addition to frequent primary resistance, most EPO or darbepoetin responders eventually relapse in 70% of the cases without progression to higher-risk MDSs but simply loss of sensitivity of erythroid progenitors to EPO or darbepoetin.[15]

After primary or secondary EPO or darbepoetin failure in lower-risk MDSs, adding granulocyte colony-stimulating factor to this treatment induces 20% to 30% of responses, although fewer when high EPO or darbepoetin doses are used.[11] In the absence of del(5q), lenalidomide yields TI rates of ~25%,[16] reaching 40% if lenalidomide is combined with EPO or darbepoetin (in spite of resistance to such treatment), but with a median duration <1 year[17]; 30% to 50% response rates have been reported with hypomethylating agents (HMAs), including with less-intensive HMA regimens.[18,19] However, in 2 European studies, which included mostly anemic lower-risk MDSs having failed EPO or darbepoetin, RBC TI was achieved in only ~20% of patients.[20,21] Antithymocyte globulin, with or without cyclosporine, also yields erythroid response in 30% to 40% of highly-selected lower-risk patients.[22,23] Thus, treatment options in patients failing EPO or darbepoetin remain relatively limited.

Newer treatments are being proposed in those patients.[24] Among them, luspatercept, a transforming growth factor-β (TGF-β) ligand trap, is probably the most promising, especially in MDS-RS.

Alterations of TGF-β signaling in MDSs and activin receptor II ligand traps

The TGF-β superfamily includes a large number of proteins, that is, activins, growth differentiation factors (GDFs), and bone morphogenetic proteins (BMPs), mainly secreted by hematopoietic and mesenchymal stem cells, which play a major role during signaling in the bone marrow hematopoietic stem cell niche. The TGF-β family signals through 7 different type I and 5 different type II transmembrane receptors.[25] Type I receptors (ALK2, ALK4, and ALK7), and activin receptor IIA (ActRIIA), are typically the mediators of the activins effect.[26] ActRIIs are shared by some of the BMPs and GDFs.[27] Activin signaling is carried out through formation of a ternary complex between the ligand and the type II and the type I receptors, which ultimately phosphorylates SMAD proteins.[25,26] (Figure 1A)

TGF-β signaling normally inhibits terminal erythroid differentiation by induction of apoptosis and cell-cycle arrest in erythroblasts.[28] During early erythroid maturation, parallel suppression of TGF-β signaling through reduced GDF expression and stimulation by EPO occurs (Figure 2B).[29] In MDS patients and/or MDS mouse models, activated activin A mediating apoptosis, increased TGF-β signaling, plasma GDF11, and phosphorylated Smad2/3 suggesting constitutive activation of TGF-β signaling have been observed, correlated with ineffective erythropoiesis, iron overload, and erythroid hyperplasia. *SMAD2/3* inhibition by small hairpin RNA and pharmacologic inhibition of TGF-β receptors can enhance hematopoiesis in MDSs in vitro.[30-32]

Compounds inhibiting the TGF-β pathway, particularly the ActRII ligand traps sotatercept (ACE-011) and luspatercept (ACE-536), have thus been explored to treat anemia of lower-risk MDSs.

Luspatercept (and sotatercept) in lower-risk MDSs

Luspatercept (and sotatercept) are ligand traps consisting of the extracellular domain of ActRIIA linked to the human immunoglobulin G_1 (IgG_1) Fc domain (Figure 2A). Although they have certain similarities, their potential to trap especially activin A differs.

Sotatercept was initially developed to increase bone mineral density in malignant bone disease or osteoporosis due its potential targeting of activin signaling.[33-35] Unexpectedly, this was accompanied by erythroid responses.[36] Improvement of ineffective erythropoiesis was subsequently shown in murine models of chemotherapy-induced anemia[37] and β-thalassemia.[38] Reduction of oxidative stress and promotion of late-stage erythropoiesis, mainly as a result of GDF11 inhibition, were observed.[39] In healthy postmenopausal women, and in multiple myeloma, sotatercept induced a sustained increase in Hb.[40-42] The drug appears to also act indirectly on erythropoiesis via modulation of marrow stromal cells, whereas there is no direct effect on the proliferation of erythroid progenitors.[43] In a phase 2 escalating dose trial of sotatercept in 74 anemic lower-risk MDSs refractory to erythropoietic stimulating agents (and, in 50% patients, to HMA and/or lenalidomide), 48.6% achieved HI-E, including 46.8% of those with high transfusion burden and 58.3% of those with low transfusion burden. Response rates were higher among patients with MDS-RS (58.8% vs 22.2% in other lower-risk MDS).[44] The maximum tolerated dose was 1 mg/kg every 3 weeks, with very limited side effects.

For luspatercept, in vivo studies with its murine ortholog RAP-536 showed rapid and robust dose-dependent increase in Hb and reticulocyte counts and normalization of the marrow myeloid-to-erythroid ratio in the NUP98/HOXD13 MDS mouse model.[31] By reducing the expression of GDF11 and ActRIIB, RAP-536 particularly promoted differentiation of cells already committed to the erythroid lineage, corrected erythroid hyperplasia and ineffective erythropoiesis, and increased the number of erythrocytes without acceleration of leukemic progression. RAP-536 also had no impact on iron parameters, suggesting no alteration of iron homeostasis.[31]

In healthy postmenopausal women, luspatercept demonstrated sustained increase in Hb levels.[45] In a phase 2 trial in lower-risk MDS with TD anemia (generally erythropoietic stimulating agent naive), patients received luspatercept 1 to 1.75 mg/kg every 3 weeks subcutaneously for up to 5 cycles.[46] HI-E and RBC-TI responses were 61% (30 of 49 patients) and 55% (16 of 29 patients), respectively. Higher response rates were observed in MDS-RS and in patients with lower serum EPO levels. The safety profile was favorable.[46]

Because of its higher specificity for GDF11 and less activin binding (therefore of potentially less off-target effects), luspatercept rather than sotatercept has been further developed in MDSs. In a recent randomized, placebo controlled phase 3 trial (MEDALIST) in 229 TD MDS-RS (either EPO/darbepoetin refractory or with a high serum EPO level), 38% and 53% of patients who received luspatercept (1-1.75 mg/kg every 3 weeks) achieved TI and HI-E, respectively, vs 13% and 12% with placebo,[47] and luspatercept had a favorable safety profile. Median response duration to luspatercept was 30.6 weeks.

Galunisertib is an oral drug that inhibits SMAD2/3 activation, stimulates hematopoiesis in MDSs through selective inhibition of TGF-β receptor I kinase (ALK5), that is, through a different TGF-β–signaling pathway than sotatercept and luspatercept, the latter mainly restoring late stages of hematopoiesis.[39] Galunisertib yielded 30% responses in lower-risk MDSs.[48]

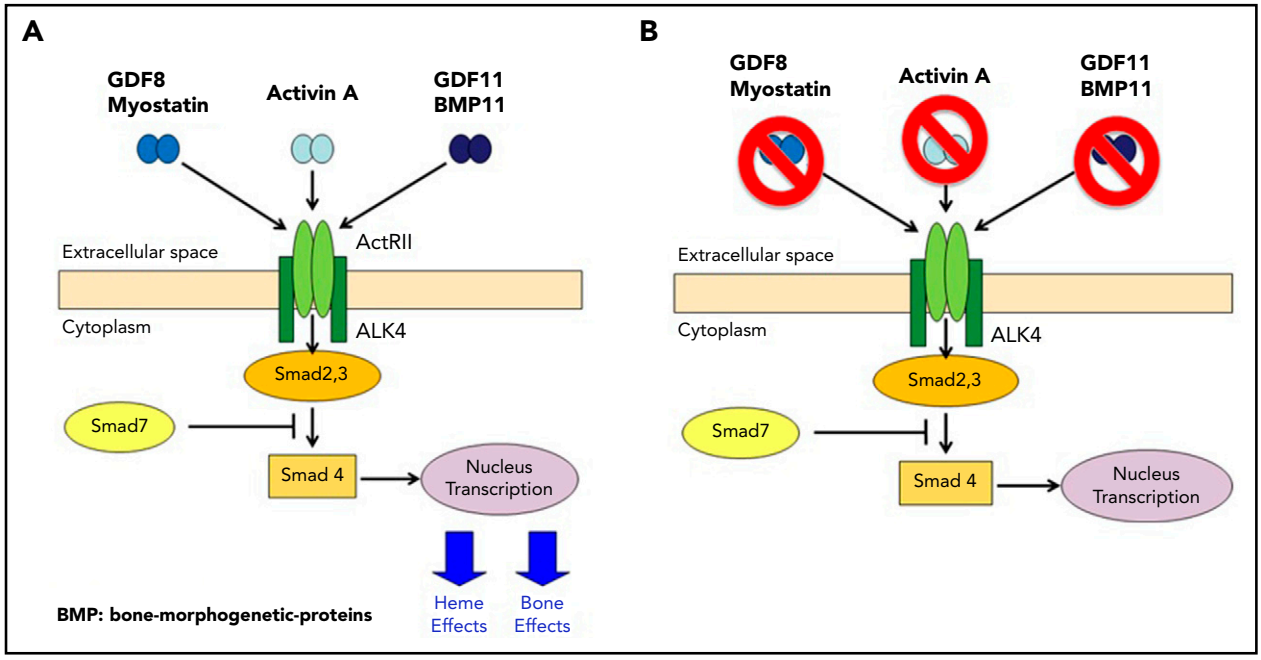

Figure 1. ActRII pathway. (A) ActRII pathway. (B) ActRII pathway inhibition.

Unanswered questions with luspatercept in lower-risk MDSs

The precise mechanisms of action of luspatercept on erythropoiesis in MDSs remains poorly defined, and further studies are needed to determine the functional consequences of inhibition of selected TGF-β superfamily members in those disorders. It is also unclear why luspatercept appears to be more effective in MDS-RS. MDS-RS are, however, characterized by larger expansion of marrow erythroblastic compartments than other lower-risk MDSs, potentially at maturation stages that could be more inhibited by some TGF-β members. Further studies are also needed to define other potential biomarkers of response.

Clinical trials will also determine whether luspatercept yields higher response rates/longer responses than EPO or darbepoetin upfront in lower-risk MDSs including MDS-RS, and whether luspatercept has additive/synergistic effects in MDS with EPO/darbepoetin (as suggested by in vitro studies),[29] lenalidomide, or galunisertib.

Finally, a potential effect of luspatercept on the disease course of lower-risk MDSs (progression or not to higher-risk MDSs and

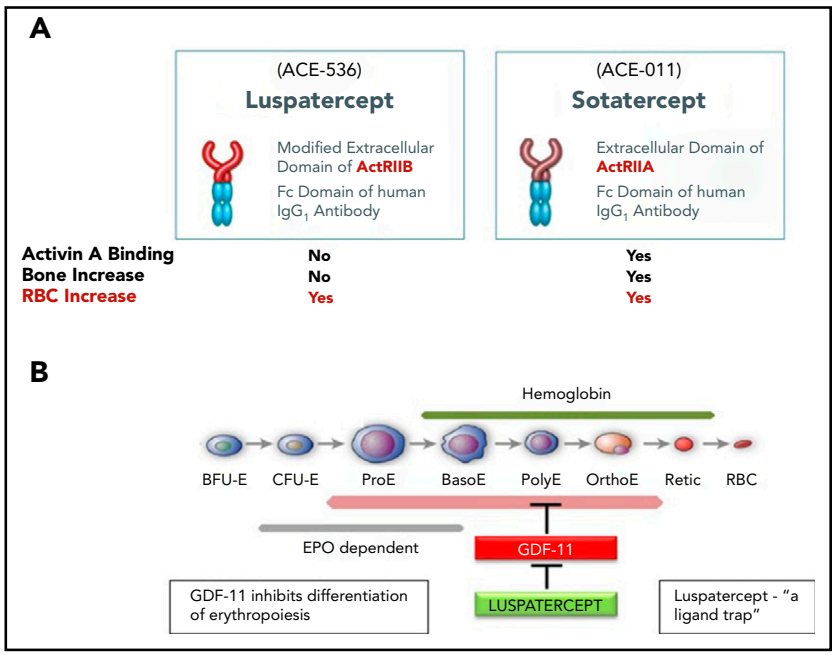

Figure 2. Luspatercept and sotatercept. (A) Molecular structure of luspatercept and sotatercept. (B) Mechanism of action of luspatercept. ACE, angiotensin-converting enzyme; BasoE, baso erythroblast; BFU-E, burst-forming unit erythroid; CFU-E, colony-forming unit erythroid; OrthoE, ortho erythroblast; PolyE, poly erythroblast; ProE, pro erythroblast; Retic, reticulocyte.

AML) will have to be analyzed. It is currently unclear whether drugs currently used after EPO or darbepoetin failure like lenalidomide, antithymocyte globulin, or HMA have such an effect on disease progression and therefore on survival.[15]

Sotatercept (and luspatercept) in PMF

Anemia is also 1 of the most frequent clinical findings in primary myelofibrosis (PMF), poorly managed with currently available drugs and associated with worse survival.[49] TGF-β signaling plays a major role in disease development in PMF: it is expressed at high levels in the bone marrow of patients and in animal models, and megakaryocytes of myelofibrosis (MF) patients release large amounts of this cytokine,[50-52] whereas inhibition of TGF-β signaling can prevent fibrosis development and reactivate normal hematopoiesis, particularly erythropoiesis, in several models.[53,54] In a phase 2 trial in MF patients,[55] 6 of 17 patients (35%) and 1 of 8 patients (12.5%) treated with sotatercept alone and combined with ruxolitinib, respectively, achieved erythroid response, with good tolerance.[55] A phase 2 study of luspatercept with or without ruxolitinib was more recently started in anemic MF patients (NCT03194542). Because spliceosome mutations like SF3B1 are also quite frequent in myeloproliferative neoplasm, their potential prognostic value for response will have to be evaluated.

Conclusions

The major therapeutic challenge in lower-risk MDSs (and often in PMF) remains improving anemia, thereby reducing RBC transfusions and cardiovascular complications, and increasing quality of life. Current treatments of anemia in MDSs have inconstant and generally transient efficacy. The activin receptor ligand trap luspatercept represents a promising alternative for EPO- or darbepoetin-refractory patients that often carry defects downstream of EPO activity. Interestingly, comparable results have been observed with luspatercept in β-thalassemia, suggesting previously unrecognized commonalities between the 2 diseases.[56,57]

Further studies are necessary to determine the place of luspatercept in the treatment of anemia of non-RS lower-risk MDSs (second line? first line?), possibly in combination with other drugs and also in PMF, and the precise mechanisms of action of this drug.

Authorship

Contribution: P.F., J.J.K., and U.P. wrote the paper.

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ORCID profile: J.J.K., 0000-0002-8121-438X.

Correspondence: Pierre Fenaux, Service Hématologie Séniors, Hôpital St. Louis, Assistance Publique–Hôpitaux de Paris and Université Paris Diderot, 75475 Paris, France; e-mail: pierre.fenaux@aphp.fr.

Footnote

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