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Should we move past erythropoietin-stimulating agent monotherapy in lower-risk myelodysplastic syndromes?

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MDS are clonal stem cell disorders characterized by ineffective hematopoiesis with progressive bone marrow failure resulting in cytopenias. Anemia is the most prevalent cytopenia and 25-30% of patients present with transfusion dependence at diagnosis.[1] Erythropoietin-stimulating agents (ESAs) are often the first-line therapy in lower-risk disease to reduce symptoms from anemia and eliminate or delay transfusion dependence.[1,2] ESA response rates are substantially lower (< 25%) in patients with significant transfusion dependence and endogenous serum erythropoietin levels above 200 U/L.[3] Most guidelines state that ESAs should not be used when EPO levels exceed 500 U/L.[4] Thus there is a need to improve upon current treatment strategies for this group of patients.

In this issue of Haematologica, Mei et al., report the results of their multicenter, single-arm, prospective trial evaluating recombinant human erythropoietin (rhEPO) plus all-trans retinoic acid (ATRA) and testosterone undecanoate for the treatment of anemia and transfusion dependence in patients with lower-risk MDS.[5] Biological rationale exists for combining these 3 agents. ATRA, a standard component of therapy for acute promyelocytic leukemia, promotes hematopoietic cell differentiation and enhances erythroid colony formation.[6] As monotherapy, ATRA has a suboptimal improvement in anemia for patients with MDS with better results observed in combination with rhEPO.[6,7] Androgens stimulate erythropoiesis by increasing the sensitivity of erythroid progenitor cells to erythropoietin[8] and when also combined with ATRA, may improve anemia in patients with MDS.[9] Encouraged by these findings, the authors hypothesized that this triple combination therapy might improve erythroid response rates.

Eligible patients received rhEPO 10,000 IU/day, ATRA 25 mg/m^2/day and oral testosterone undecanoate 80 mg twice daily for 12 weeks with the primary endpoint of hematological improvement-erythroid (HI-E) using 2006 IWG criteria.[10] If response was demonstrated at 12 weeks, treatment was continued until progression or unacceptable toxicity. In total, 52 patients with primarily untreated lower-risk disease received treatment and were eligible for analysis with a median age of 65 years and a median Hb of 62 g/L (range 40-91 g/L). At baseline, 56% had a serum EPO level of greater than 500 U/L, 40% harbored mutations in *SF3B1* and 52% were transfusion dependent. With a median follow up of only 20 weeks, 32 (62%) achieved HI-E and notably, 17 out of 29 patients (59%) with a baseline serum erythropoietin level of >500 U/L also responded. The post treatment median Hb in responders was 95 g/L (range 68-152 g/L) compared with 73 g/L in non-responders (range 46-91 g/L). Of the transfusion dependent patients, 48% achieved and maintained transfusion independence for $\geq$ 12 weeks. Lower response rates were demonstrated in patients with *ASXL1* mutations (33% mutated versus 70% wild type). Importantly, this regimen was well-tolerated and had a toxicity profile consistent with the individual agents with 4 reported grade 3 treatment-related adverse events (infection in 3 patients, deep vein thrombosis in 1 patient) although rates of virilization in women were surprisingly absent.

This study is notable for several reasons. First, it combines three previously uncombined agents to target anemia in MDS. Additionally, response rates did not differ between *SF3B1* mutated (71%) and wild type (55%) disease in contrast with 70% (*SF3B1* mutated) and 45% (*SF3B1* wild type) achieving transfusion independence with luspatercept in the COMMANDS trial.[11] Lastly, high response rates were achieved in patients with very elevated EPO levels (excluded from most

trials) and in transfusion dependent patients. However, transfusion density was not provided, and their definition of transfusion dependence was only a minimum of 1 packed red blood cell unit per 8 weeks compared with other trials.[11-13]

While interesting and certainly promising, this triplet therapy is not yet ready for prime time without comparative data against monotherapy agents like luspatercept and imetelstat in non-Asian patients. For one, the EPO doses used (70,000 IU per week) are much higher than typical starting doses and may play the heavy-hitting roles in these modestly defined responses (8 weeks of transfusion independence). Second, response durability was not provided—an important endpoint in assessing efficacy. Third, fatigue was an adverse event in 38.4%, when amelioration of fatigue is the goal of most erythroid stimulating approaches. Fourth, external validity remains to be proven since the median baseline hemoglobin levels were more than 10g/L lower compared with the pivotal luspatercept and imetelstat trials.[11-13] Lastly, the highest hemoglobin levels achieved with HI-E were very modest, possibly without impact on quality of life, given the importance of a Hb threshold of 100 g/L.[14]

In summary, the prospective single-arm trial presented by Mei and colleagues builds upon the current paradigm of ESA monotherapy for the treatment of anemia in patients with lower-risk MDS, in particular, for patients with baseline serum EPO levels exceeding 500 U/L. It is worthy of further investigation and comparative analysis with luspatercept, imetelstat (table 1), hypomethylating agents and others.

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Table 1. Recent trials for the treatment of anemia in patients with myelodysplastic syndromes

Study population	Intervention	Primary Endpoint	Baseline/pretransfusion Hemoglobin (median)	Primary Result
Current study: MDS (IPSS-R very low, low or intermediate) Baseline Hb< 100 g/L without requirement for TD May have received previous ESA, no EPO level cut-off[5]	RhEPO + ATRA + testosterone undecanoate	TI for at least 12 weeks with increase in Hb ≥15 g/L lasting for ≥8 consecutive weeks	62 g/L (range 40 to 91 g/L)	62% (95% CI, 48–74%)
MEDALIST: MDS (IPSS-R very low, low or intermediate) with ring sideroblasts (≥15% ring sideroblasts or ≥5% if *SF3B1* mutated) RBC-TD (≥2 units/8 weeks during 16-week period) Refractory to or ineligible for EPO (>200 U/L in EPO naïve)[12]	Luspatercept versus placebo	TI for ≥8 weeks during first 24 weeks	Luspatercept: 76 g/L (range 60 g/L to 10 g/L) Placebo: 76 g/L (range 50 g/L to 90 g/L)	Luspatercept: 38% (95% CI, 30–46) Placebo: 13% (95% CI, 6–23) P < 0.001
COMMANDS: MDS (IPSS-R very low, low or intermediate) RBC-TD (2-6 units per 8 weeks for at least 8 weeks) ESA-naïve with EPO level <500 U/L)[11]	Luspatercept versus epoetin alpha	TI for at ≥12 weeks with a concurrent mean Hb increase of at least 15 g/L during first 24 weeks	Luspatercept: 78 g/L (IQR, 71 g/L to 82 g/L) Epoetin alpha: 78 g/L (IQR, 71 g/L to 83 g/L)	Luspatercept: 60% Epoetin alpha: 35% P <0.0001
IMerge: MDS (IPSS low or intermediate-1) RBC-TD (≥4 units over 8-weeks during 16-week period) Relapsed/refractory to or ineligible for ESAs (EPO >500 U/L)[13]	Imetelstat versus placebo	Proportion of patients who had RBC-TI for ≥8 consecutive weeks	Imetelstat: 79 g/L (IQR, 73 g/L to 83 g/L) Placebo: 78 g/L (IQR, 74 g/L to 84 g/L)	Imetelstat: 40% (95% CI, 31–50) Placebo: 15% (95% CI, 7–27) P=0.0008

Abbreviations: MDS, myelodysplastic syndromes; IPSS-R, Revised International Prognostic Scoring System; IPSS, International Prognostic Scoring System; TD, transfusion dependent; TI transfusion independent