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DIGITAL HUB

B- THALASSEMIA & MYELODYSPLASTIC SYNDROME

EHA-2024 Medical debriefing and breakdown of B-Thalassemia and Myelodysplastic Syndrome.

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A GLOBAL EPIDEMIOLOGICAL OVERVIEW

B-Thalassemia

Beta thalassemia is prevalent in the MENA region, with carrier rates ranging from 2-10% across countries like Iran, Saudi Arabia, Egypt, Lebanon, Jordan, Morocco, and Tunisia. Annually, there are around 1,000 new cases in Iran and Saudi Arabia, and several hundred in Egypt. Public health efforts include national screening programs and genetic counseling, with premarital screening mandatory in some countries. Advances in medical care have improved life expectancy, though access varies. Research initiatives focus on improving diagnosis and treatment, including experimental gene therapies, highlighting the substantial burden and ongoing efforts to manage beta thalassemia in the region.

MYELODYSPLASTIC SYNDROME-MDS

Myelodysplastic syndromes (MDS) in the GCC countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the UAE) predominantly affect older adults, with incidence rates similar to global trends, around 2-4 cases per 100,000 annually in Saudi Arabia. MDS is more common in men and presents with symptoms like anemia and infection. Diagnosis and treatment follow international guidelines, including bone marrow examinations and advanced therapies like stem cell transplantation, though access varies. Efforts to improve data collection and research are ongoing to enhance understanding and management of MDS in the region.

EXPERT TESTIMONIALS

INSIGHTS ON BETA-THALASSEMIA & MDS FROM LEADING AUTHORITIES

"As someone deeply invested in healthcare and medical advancements, I found the 1st edition of the digital magazine on Beta-Thalassemia and Myelodysplastic Syndrome to be a comprehensive and enlightening resource. The magazine not only delves into the complexities of these conditions but also offers practical insights into treatment options, current research, and patient experiences.This magazine is a testament to the power of knowledge in improving lives and advancing medical care."

Dr Asma Al Olama
President
Emirates Society of Hematology

"The 1st edition of the digital magazine on Beta-Thalassemia and Myelodysplastic Syndrome is an invaluable resource. It combines in-depth scientific analysis with real world patient experiences, offering a balanced and insightful perspective. The magazine's thorough coverage of treatment options, ongoing research, and support resources provides much-needed clarity and hope for patients, caregivers, and healthcare professionals alike."

Dr Ahmad M. Tarawah
President
Middle East and North Africa Hematology League

EHA-2024 Medical debriefing and breakdown of B-Thalassemia and Myelodysplastic Syndrome

B-Thalassemia

1 SPLENECTOMY AND B-THALASSEMIA IN FRANCE: BENEFITS, RISKS AND PRACTICES

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Background:

The role of splenectomy in β-thalassemia management is difficult to define because of the potentially poor risk/benefit ratio. Expected improvement in anemia and/or transfusion requirements post-surgery can be offset by a higher risk of thromboembolic (TE) complications and/or infections.

Aims:

The aims of this study were to analyze the occurrence of TE and spleen-related infectious complications in a large population of β-thalassemia patients over time according to disease phenotype and spleen status.

Methods:

Since 2005, the French national Thalassemia Registry prospectively collects data from patients with β-thalassemia major (TM, transfusion-dependency <4 years) or intermedia (TI) nationwide. In this study, we analyzed data collected until December 31st, 2022, or date of death or hematopoietic stem cell transplant, whichever came first. All TE events (venous or arterial thrombosis (VT, AT), pulmonary embolism (PE), stroke, pulmonary arterial hypertension (PAH) and infections by encapsulated bacteria occurring after splenectomy or during follow up for non-splenectomised patients were collected.

Results:

Data from 834 patients totalizing 20 200 patient/years (PY) of observation was analyzed (Figure 1A). Overall, 38% (n=322) of patients underwent splenectomy. A dramatic decrease over time in the proportion of splenectomised patients was evidenced (from 80% in the 60s to 30% in the 2000s), along with a decrease of age at splenectomy (17vs 7 years).Comparison between patients with TM and TI showed a significantly greater proportion of splenectomy in TM patients(41%vs 33%, p=0.03) and a younger age at splenectomy (9.2 (6.2; 14.2)vs 11.7 (7.0; 19.3), p=0.007). Median delay between splenectomy and last follow up was however comparable between groups. Regarding infections, only 4 were reported, all in splenectomised patients (3 TM), yielding a very low overall incidence of 0.04 PY. A total of 92 TE events occurred in 59 patients, of which 55 were splenectomised (p<0.0001). Median delay between splenectomy and 1st TE event was 18.7 (8.6; 24.1) years and was comparable between TM and TI patients (Figure 1B). In the splenectomised group, most patients had only 1 event (n=38; 11.8%) but 5.3% (n=17) had 2 or more. TE events included 27 VT (31.4%), 19 PE (22.1%), 15 cases of PAH (17.4%), 11 portal thrombosis (12.8%), 6 thrombosis associated with a central device (7%), 6strokes (7%) and 2 AT (2.3%). Overall, TE events were significantly more frequent in TI patients, whether splenectomized or not, compared to TM (incidence of 0.64 and 0.31 respectively). Portal thrombosis was found in 3.4% patients of the splenectomized group, a higher proportion compared to non-thalassemic splenectomized patients (2%), warranting systematic echographic screening post-surgery and potentially prophylactic treatment. Overall incidence of TE events in the studied cohort was 0.79 PY in splenectomized patients compared to 0.06 PY in non splenectomized patients, resulting in a dramatically increased risk following splenectomy (x13). Highest incidence was evidenced in patients with TI following splenectomy (1.39 PY) compared to 0.48 PY in TM patients, raising the question of a protective effect of regular transfusion.

Summary/Conclusion:

This study confirms in a large cohort followed longitudinally that TE events occur with a high incidence following splenectomy in β- thalassemia patients. Benefice/risk ratio has changed over time and indication of splenectomy should be discussed on a case-by-case basis, particularly in TI patients. Whether transfusions may be protective against TE events require further analysis.

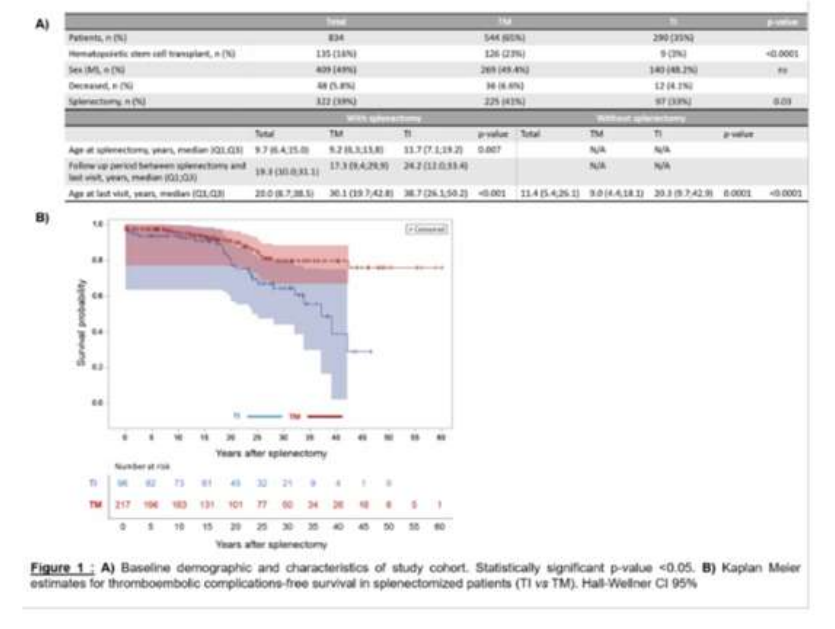

Figure 1 : A) Baseline demographic and characteristics of study cohort. Statistically significant p-value <0.05. **B)** Kaplan Meier estimates for thromboembolic complications-free survival in splenectomized patients (TI *vs* TM). Hall-Wellner CI 95%

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PAPER: SPLENECTOMY AND B-THALASSEMIA IN FRANCE: BENEFITS, RISKS AND PRACTICES

2 SAFETY DATA FROM THE DOSE-FINDING COHORTS: A PHASE 2A STUDY OF LUSPATERCEPT IN PEDIATRIC PATIENTS WITH BETA-THALASSEMIA

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Background:

β-thalassemia is characterized by ineffective erythropoiesis and anemia of varying severity, with many patients (pts) requiring lifelong red blood cell (RBC) transfusions and iron chelation therapy. There is an unmet need among pediatric pts with β thalassemia for treatments that reduce anemia, minimize chronic RBC transfusions, and mitigate secondary iron overload. Luspatercept has been shown to decrease transfusion burden in adult pts with transfusion-dependent (TD) β-thalassemia, and to durably increase hemoglobin (Hb) levels in adult pts with non-TD (NTD) βthalassemia.

Aims:

To evaluate safety and determine the recommended dose (RD) of luspatercept in pediatric pts with TD and NTD β thalassemia (NCT04143724, EudraCT 2019-000208-13).

Methods:

Eligible pts are 6 to <18 y of age with TD or NTD β-thalassemia. TD pts must have received ≥4 RBC transfusions in the 24 wk pre-enrollment (no transfusion-free period ≥42 d and have a regular history of transfusions for ≥2 y). NTD pts (ex-US sites only) must have received <4 RBC transfusions in the 24 wk pre-enrollment, not be on regular transfusions, be RBC transfusion-free for ≥8 wk pre-enrollment, and have mean baseline Hb ≤10 g/dL. The study is staggered and in 2 parts: Part A (pts 12 to <18 y of age) and Part B (pts 6 to <12 y of age). In the dose-finding phase of Part A, TD pts received luspatercept subcutaneously at 0.75 mg/kg (Cohort 1) or 1.0 mg/kg (Cohort 2) Q3W for ≤4 cycles to determine the RD. NTD pts are eligible to receive luspatercept in a dose-confirmation cohort designed to mirror TD Cohorts 1 and 2. A dose-expansion cohort will follow for NTD pts at the RD; for TD pts, a dose-expansion cohort is currently recruiting. Part B will be initiated following recommendation by the Data Monitoring Committee based on ≥12 mo of safety data from Part A. Pts who benefit may continue treatment for up to 5 y. The primary objectives of the trial are to determine safety, tolerability, and pharmacokinetics (PK) of luspatercept in TD and NTD pts. Safety assessments include adverse events (AEs) and the frequency of dose-limiting toxicities (DLTs). Secondary objectives include evaluating mean change in RBC transfusion burden (TD pts), mean change in Hb level (NTD pts), iron parameters, and immunogenicity. The safety data reported here are for TD pts from the dose-finding phase of Part A.

Results:

As of October 2, 2023, 12 TD pts had received luspatercept (6 pts in each dose-finding cohort). Median age was 14 y in both cohorts and pt demographics were similar. Median (range) treatment duration was 651.5 (405–718) d in Cohort 1 and 219.0 (21–551) d in Cohort 2; pts received a median (range) of 31.0 (19–36) and 10.5 (1–27) doses, respectively. Dose titrations up to 1.25 mg/kg occurred in both cohorts (4/6 pts in Cohort 1 and 1/6 pt in Cohort 2), with no dose reductions or DLTs reported. Treatment-emergent AEs (TEAEs) were reported in all pts, with 2/6 pts in Cohort 1 and 4/6 pts in Cohort 2 experiencing TEAEs related to luspatercept (Table). There were no grade 3/4 TEAEs related to luspatercept in any cohort, and no TEAEs led to luspatercept discontinuation.

Summary/Conclusion:

Safety data from this dose-finding phase in pediatric pts with TD β-thalassemia revealed a safety profile of luspatercept consistent with that observed in adults, with no DLTs or TEAEs resulting in treatment discontinuation. Recruitment is open for the NTD dose-confirmation and TD expansion cohorts. PK and efficacy assessments are ongoing.

Table:

TEAEs considered by the investigator to be treatment-related, per patient

Cohort	Patient	TEAE	Grade	Resolution
Cohort 1 (0.75 mg/kg)	1	Marrow hyperplasia[a]	1	Ongoing
		Splenomegaly[b]	1	Ongoing
		EMH[c]	1	Ongoing
	2	Injection site pruritus	1	Resolved
Cohort 2 (1.0 mg/kg)	3	Back pain	1	Resolved
	4	Pyrexia	2	Resolved
		Dyspnea	1	Resolved
	5	Vision blurred	1	Resolved
	6	Hypertension	2	Resolved

[a]Asymptomatic. [b]Pt had previous history of splenomegaly. [c]Asymptomatic, developed after 589 d on treatment. d, day; EMH, extramedullary hematopoiesis; Pt, patient; TEAE, treatment-emergent adverse event.

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PAPER: SAFETY DATA FROM THE DOSE-FINDING COHORTS: A PHASE 2A STUDY OF LUSPATERCEPT IN PEDIATRIC PATIENTS WITH BETA-THALASSEMIA

3 CHARACTERIZING PATTERNS OF TRANSFUSION BURDEN (TB) REDUCTION IN PATIENTS (PTS) WITH TRANSFUSION-DEPENDENT (TD) BETA-THALASSEMIA TREATED WITH LUSPATERCEPT IN THE BELIEVE TRIAL

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Background:

In the BELIEVE trial evaluating luspatercept in TD β-thalassemia (NCT02604433), 21.4% of pts treated with luspatercept achieved the primary endpoint of ≥33% TB reduction from baseline (BL) in wk 13–24, vs 4.5% for placebo (PBO) (Cappellini MD, et al. N Engl J Med 2020;382:1219–1231). Interestingly, many pts not achieving the primary endpoint showed meaningful reductions in RBC TB with continued luspatercept therapy beyond wk 24, suggesting that pts considered non-responders may benefit from continued treatment (Piga A, et al. HemaSphere 2021;5[suppl 2]:EP1306). Better understanding of patterns of TB reduction in the first year of luspatercept treatment and identification of response predictors are needed to inform treatment decisions and maximize pt benefit.

Aims:

To characterize the timing, magnitude, and durability of TB reductions in pts treated with luspatercept in the BELIEVE study and identify predictors of response.

Methods:

In BELIEVE, adult pts with TD β-thalassemia were randomized to receive luspatercept or PBO every 3 wk for ≥48 wk. TB reduction of 20% was identified as the minimum for this sub analysis based on the mean TB reduction from BL over 48-wk intervals (wk 1–144) in the luspatercept group (n=224). This sub analysis includes pts who completed ≥48 wk of treatment, including those randomized to receive luspatercept or PBO and those randomized to PBO who crossed over to receive luspatercept after unblinding. For crossover pts, treatment timing was defined from initiation of luspatercept therapy. Change in TB was categorized as (i) no reduction (or increase), (ii) >0% to <20%, (iii) ≥20% to <33%, and (iv) ≥ 33% reduction from BL for early (wk 1–24) and late (wk 25–48) time points. BL characteristics and erythropoiesis biomarkers were evaluated in pts achieving ≥20% TB reduction at early vs late time points vs pts not achieving ≥20% TB reduction at either timepoint to identify response predictors. Data cutoff was the last pt last visit in the BELIEVE trial (Jan 5, 2021).

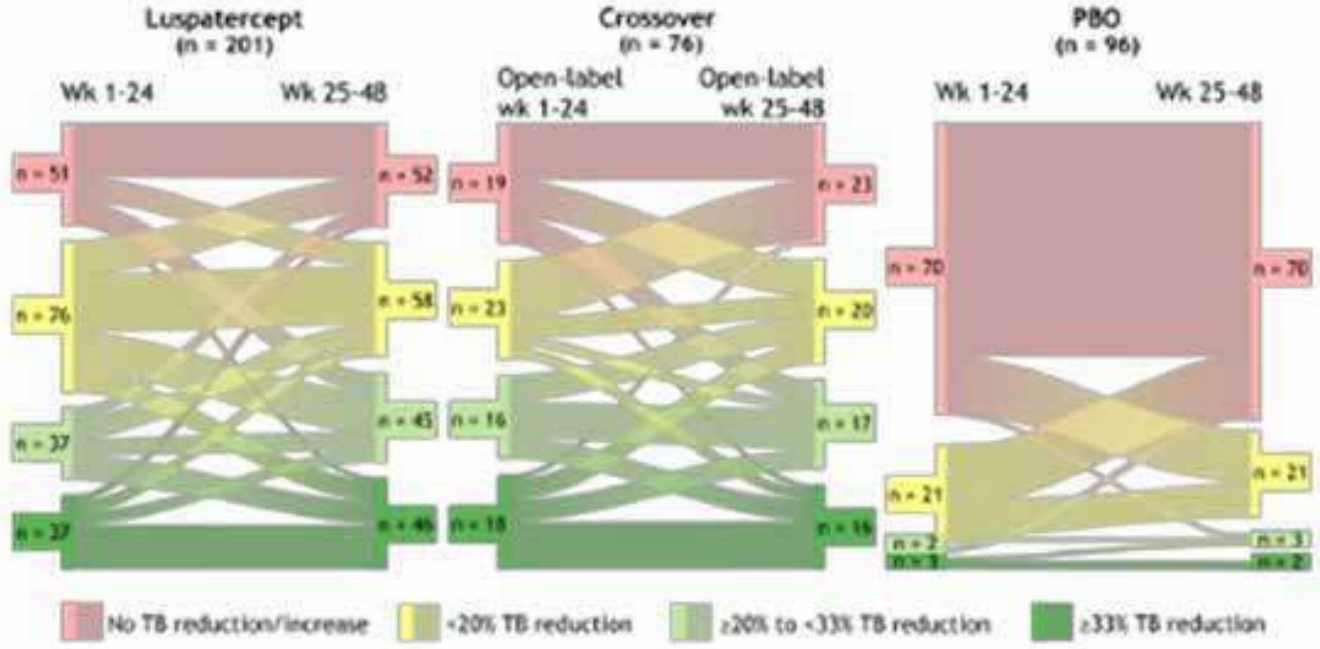
Results:

The PBO group (n=96) showed minimal change in response with longer treatment: of the 91 pts with no reduction or <20% TB reduction from BL in wk 1–24, only 2 (2%) achieved ≥20% TB reduction in wk 25–48 and no pts deepened their response to ≥33% reduction. In contrast, deepened response was seen in the luspatercept (n=201) and crossover (n=76) groups: 42/127 (33%) luspatercept and 9/42 (21%) crossover pts with no reduction or <20% TB reduction in wk 1–24 deepened their response to ≥20% TB reduction in wk 25–48. In addition, the luspatercept and crossover groups showed durability of TB reduction, with 43/74 (58%) luspatercept pts and 20/34 (59%) crossover pts with TB reduction ≥20% in wk 1–24 maintaining or deepening their response category in wk 25–48 (Figure). In the analysis of response predictors, pts in the luspatercept and crossover groups with ≥20% TB reduction at early or late timepoints were more likely to have undergone splenectomy than not; no such trend was observed in pts with <20% TB reduction. Pts with ≥20% TB reduction at early or late time points tended to have lower erythropoietin and higher reticulocyte counts at BL than pts with <20% TB reduction.

Summary/Conclusion:

Luspatercept and crossover pts in BELIEVE with no reduction or <20% TB reduction in wk 1–24 could achieve ≥20% TB reduction in wk 25–48, which was rare for PBO.** Continuing luspatercept therapy beyond 24 wk in pts who initially show <20% TB reduction may result in improved responses and maximize pt benefit.

Figure: Changes in magnitude of RBC TB reduction from BL with continued treatment in patients in the BELIEVE trial



BL, baseline; PBO, placebo; RBC, red blood cell; TB, transfusion burden; wk, week.

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PAPER: CHARACTERIZING PATTERNS OF TRANSFUSION BURDEN (TB) REDUCTION IN PATIENTS (PTS) WITH TRANSFUSION-DEPENDENT (TD) BETA-THALASSEMIA TREATED WITH LUSPATERCEPT IN THE BELIEVE TRIAL

4 PREDICTING AND EVALUATING RESPONSE TO LUSPATERCEPT IN TRANSFUSION-DEPENDENT B THALASSEMIA: NEW INSIGHT FROM A REAL-LIFE EXPERIENCE.

Daniele Lello Panzieri*[1, 2], Guido Ausenda1, Natalia Scaramellini[2, 3], Dario Consonni[4], Francesca Granata[2], Nancy Caponio[2], Lorena Duca[2], Simona Leoni[1, 2], Silvia Elli[1, 2], Marta Ferraresi[1, 2], Elena Cassinerio[2], Greta Rossi[1], Cristina Curcio[5], Milena Agata Irrera[5], Elena Trombetta[6], Marta Tornese[6], Giovanna Graziadei[2], Maria Domenica Cappellini[2], Rayan Bou-Fakhredin[2, 3], Valentina Brancaleoni[2], Irene Motta[2, 3]

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Background:

Luspatercept is a new erythropoiesis-stimulating agent approved for the treatment of anemia in adults affected by transfusion-dependent β-thalassemia (TDT). Up to date, only a few reports of real-life experiences have been published, and no predictive factors for the response have been identified.

Aims:

The aim of this study was to evaluate the effectiveness of luspatercept in TDT patients in a real-life setting and to identify different profiles of response by analyzing hematological and erythropoietic parameters.

Methods:

As of October 31, 2023, 48 patients regularly followed at our center in Milan received at least one dose of luspatercept. We herein present data of those who received the treatment for at least 12 weeks. A reduction in the transfusion burden ≥33% in any 12-week interval defined a full response (FR), while a reduction <33% defined a non-response (NR). Blood samples for hematological and erythropoietic parameter analysis at baseline and at fixed doses were collected. In a subset of patients, flow cytometry for the presence and proportion of F-cells was performed. Statistical analysis was conducted using Stata 17.

Results:

Thirty-one patients have been included in the study. The median age was 40 years, and 55% (17/31) were females. One third (10/31) were splenectomized. Regarding the genotype, 9/28 (32%) were β0/β0, 1/28 HbE/β-thalassemia and three were ongoing. 21/31 (68%) of patients had a transfusion burden >15 units in the 24 weeks before treatment initiation. Twenty-six out of 31 (84%) received luspatercept for at least 24 weeks. 8/31 (26%) showed a reduction in TB of ≥33% in the weeks 13-24, similarly to the primary endpoint of the phase 3 trial. Fourteen were FR and 17 NR in any 12-week interval. Overall, the mean pre-transfusion hemoglobin (pt-Hb) increased under treatment (9.1±0.5 g /dL vs. 9.3±0.5 g/dL, p=0.02), but the increase was significant only in the FR group (9.0±0.6 g/dL before treatment vs. 9.6±0.5 g/dL during treatment, p=0.05). FR patients experienced a significant reduction in the transfusion burden, from 0.7±0.2 unit/week in the 24 weeks before beginning the treatment to 0.5±0.2 unit/week during the treatment, p=0.02. The only hematological parameter capable of predicting the response to luspatercept with the ROC curve analysis was the baseline value of fetal hemoglobin (HbF), with an area under the curve (AUC) of 0.85 (CI95% 0.69-1.00). A statistical cut point of baseline HbF of 0.6 g/dL provided a positive predictive value of 85% (CI95%: 57-97) and a negative predictive value of 88% (CI95%: 64-98). An increase in HbF during treatment was also observed in both groups; however, the FR reached significantly higher values than the NR at 24 weeks, 21.1% (8.9-59.1) vs. 8.9% (3.2-21.2), respectively, p=0.0005. The median absolute value of HbF in FR was 2.1 g/dL at 24 weeks. In the regression analysis, the trend in HbF increase was cubic. FR and NR had a similar pattern, with an initial rise reaching a plateau around week 16.

Preliminary data of flow cytometry show an increase in F-cells in responders during the treatment (Figure 1).

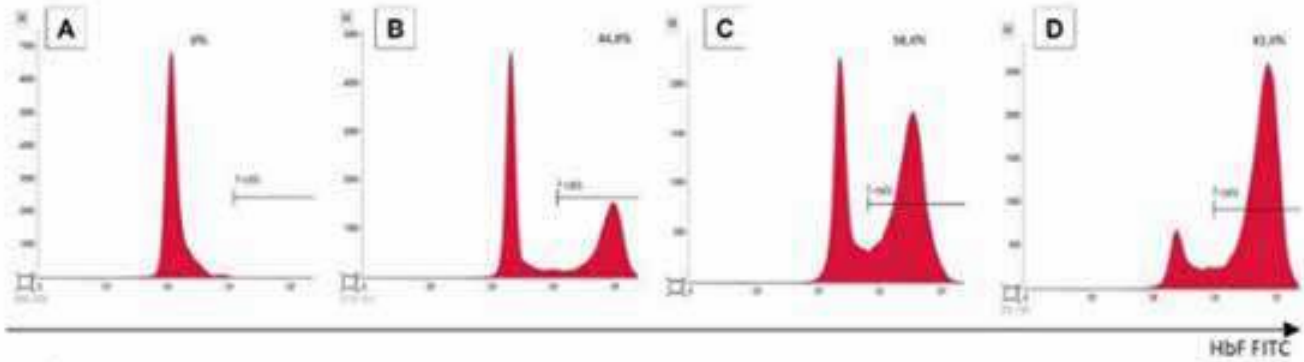

Figure 1. Flow cytometry of peripheral blood from a responder patient. The percentage of F-cells is show. In panel A the negative control is shown, panels B, C and D show respectively the percentage of F-cells at baseline (week 0), at week 6 and at week 12.

Summary/Conclusion:

In this study, we confirmed the effectiveness of luspatercept for the treatment of anemia in a real-life setting. Particularly, the increase in pre-transfusion hemoglobin has a strong impact on clinical practice, given the evidence of the deleterious effect of chronic anemia. HbF levels at baseline and their trend are a predictors and marker for response.

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PAPER: PREDICTING AND EVALUATING RESPONSE TO LUSPATERCEPT IN TRANSFUSION-DEPENDENT Β THALASSEMIA: NEW INSIGHT FROM A REAL-LIFE EXPERIENCE.

5 OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANT IN BETA THALASSEMIA MAJOR: SINGLE CENTER EXPERIENCE FROM A LOW AND MIDDLE INCOME COUNTRY

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Background:

Beta thalassemia major (BTM) is the most common hemoglobinopathy, and the mean life expectancy of BTM patients in Pakistan is around 10 years. Most patients cannot afford life lifelong blood transfusions and iron chelation; hence, they succumb to early death. Hematopoietic stem cell transplantation (HSCT) has emerged as a curative treatment for BTM.

Aims:

To determine the outcome of HSCT in BTM patients in resource-constrained settings.

Methods:

This retrospective study analyzed the data of 118 cases of BTM undergoing HSCT after myeloablative conditioning with modified protocol 26 at the AFBMTC from April 2018 to April 2023

Results:

The mean age at the time of HSCT was 85.7±33.6 months. Eighty-one (68.6%) cases were in Pesaro Class III. Mortality at day 100 was 14(11.9%), and overall treatment-related mortality (TRM) was 23 (19.4%). In univariate analysis, factors having a statistically significant association with TRM were graft failure (P=0.001), Pesaro class (P=0.03), Severity of aGVHD (P=0.02), and VOD (P=0.02

Summary/Conclusion:

After a median follow-up of 26.87± 16.60 months, OS and DFS rates were 80.5% and 78.0% respectively. We reported promising survival of around 80%, which can be further improved with better transfusion services, regular iron chelation, and HSCT at a younger age.

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PAPER: OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANT IN BETA THALASSEMIA MAJOR :SINGLE CENTER EXPERIENCE FROM A LOW AND MIDDLE INCOME COUNTRY

MYELODYSPLASTIC SYNDROME

1 SINGLE-CELL T-CELL LANDSCAPE IN MYELODYSPLASTIC SYNDROMES DURING VENETOCLAX THERAPY

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Background:

We previously showed that the cellular hierarchy of MDS HSCs predicts the mechanisms of progression after hypomethylating agent (HMA) failure and can guide the choice of targeted therapies (Nature Medicine 2022). MDS HSCs in one of two differentiation states, long-term HSCs or lymphoid-primed multipotent progenitors, have a "common myeloid progenitor (CMP) pattern" or "granulocytic-monocytic progenitor (GMP) pattern" of differentiation. These HSC differentiation states, which persist throughout the disease course and expand at progression, are driven by the recurrent activation of BCL2- and NF-κB–mediated survival pathways, respectively. Pharmacologically inhibiting these pathways depletes MDS HSCs and reduces tumor burden, suggesting that only "CMP pattern" MDS patients benefit from venetoclax-based therapies. However, "GMP pattern" MDS eventually respond to venetoclax, suggesting that other molecular and/or biological mechanisms account for outcomes after venetoclax therapy. Thus, we hypothesized that the immune system contributes to the therapeutic effect of venetoclax in MDS patients.

Aims:

To test this hypothesis, we dissected the dynamics, transcriptomes, and repertoires of bone marrow (BM) T-cell subsets and determined the degree to which these factors are correlated with patients' clinical outcomes.

Methods:

We performed flow cytometry, next-generation sequencing (seq), and single-cell RNA and T-cell receptor seq analyses of sequential paired BM samples from patients enrolled in clinical trials of venetoclax-based therapy. Overall, 64 samples from11 patients were obtained, yielding a total of 97,152 high-quality T cells and 143,884 BM mononuclear cells for analysis.

Results:

Mass cytometry analyses of sequential BM samples isolated from MDS patients receiving venetoclax revealed that CD4+ T cells expand at disease response independently of the HSCs' differentiation state (Fig 1A)(Fig 1A). To evaluate whether specific T-cell populations contribute to the clinical outcomes of patients receiving venetoclax-based therapy, we performed flow cytometry analyses of CD4+ andCD8+ T-cell subsets. Our findings revealed that naïve and stem cell–like memory (SCM) CD4+ T cells significantly expand in the BM of patients whose disease responds to therapy (Fig 1B). Notably, these CD4+ T-cell dynamics were not observed in patients receiving monotherapy with HMAs, indicating that they are specific to venetoclax therapy. Our sequential single-cell transcriptomic analyses consistently showed that SCM CD4+ T cells expanded significantly at the time of response and then contracted upon disease relapse (Fig 1C). Expanded SCM CD4+ T cells had significantly upregulated gene expression programs associated with T-cell activation and cytotoxicity during disease response but exhibited an increased exhaustion signature at disease relapse (Fig 1D). An examination of TCR distribution and dynamics confirmed that patients with venetoclax response had a higher proportion of SCM CD4+ T-cell clonotypes at baseline than patients without venetoclax response. In agreement with our phenotypic analysis, the expansion of memory CD4+ T-cell clonotypes was correlated with treatment response, whereas their contraction was observed during disease progression.

Summary/Conclusion:

A specific subset of CD4+ T cells with SCM features may contribute to the outcomes of MDS patients receiving venetoclax-based therapy independently of their HSC hierarchy. Our results highlight the potential role of adoptive immunotherapy strategies in enhancing venetoclax efficacy to improve the survival of MDS patients.

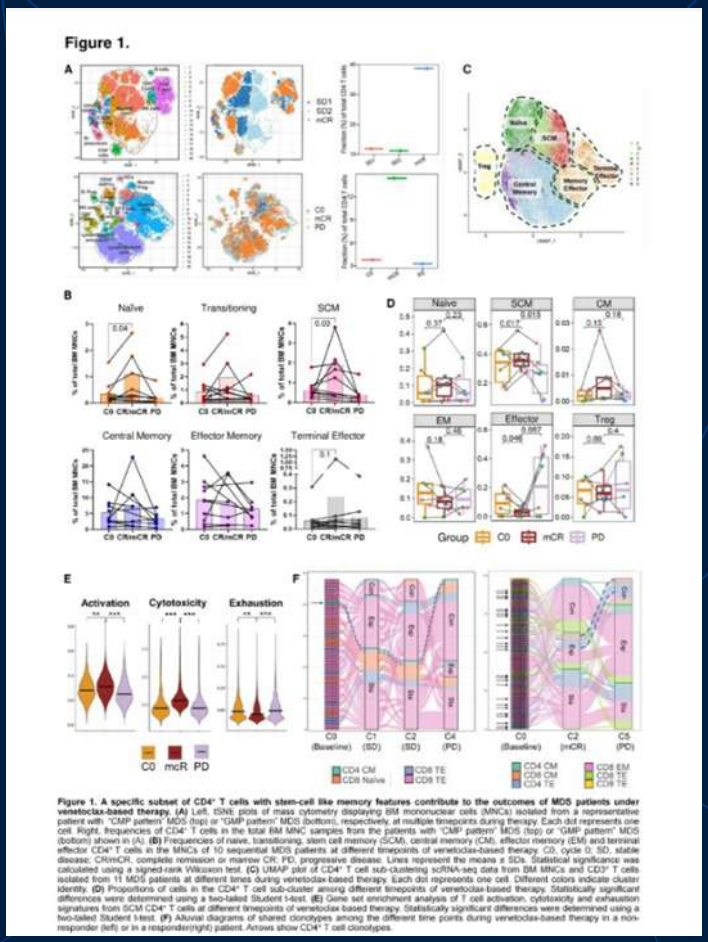

Figure 1. A specific subset of CD4+ T cells with stem-cell like memory features contribute to the outcomes of MDS patients under venetoclax-based therapy. (A) Left, tSNE plots of mass cytometry displaying BM mononuclear cells (MNCs) isolated from a representative patient with "CMP pattern" MDS (top) or "GMP pattern" MDS (bottom), respectively, at multiple timepoints during therapy. Each dot represents one cell. Right, frequencies of CD4+ T cells in the total BM MNC samples from the patients with "CMP pattern" MDS (top) or "GMP pattern" MDS (bottom) shown in (A). **(B)** Frequencies of naive, transitioning, stem cell memory (SCM), central memory (CM), effector memory (EM) and terminal effector CD4+ T cells in the MNCs of 10 sequential MDS patients at different timepoints of venetoclax-based therapy. C0, cycle 0; SD, stable disease; CR/mCR, complete remission or marrow CR; PD, progressive disease. Lines represent the means ± SDs. Statistical significance was calculated using a signed-rank Wilcoxon test. **(C)** UMAP plot of CD4+ T cell sub-clustering scRNA-seq data from BM MNCs and $CD3^+$ T cells isolated from 11 MDS patients at different times during venetoclax-based therapy. Each dot represents one cell. Different colors indicate cluster identity. **(D)** Proportions of cells in the CD4+ T cell sub-cluster among different timepoints of venetoclax-based therapy. Statistically significant differences were determined using a two-tailed Student t-test. **(E)** Gene set enrichment analysis of T cell activation, cytotoxicity and exhaustion signatures from SCM CD4+ T cells at different timepoints of venetoclax based therapy. Statistically significant differences were determined using a two-tailed Student t-test. **(F)** Alluvial diagrams of shared clonotypes among the different time points during venetoclax-based therapy in a non-responder (left) or in a responder(right) patient. Arrows show CD4+ T cell clonotypes.

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PAPER: SINGLE-CELL T-CELL LANDSCAPE IN MYELODYSPLASTIC SYNDROMES DURING VENETOCLAX THERAPY

2 REAL-WORLD DOSE ESCALATION AND OUTCOMES AMONG PATIENTS WITH LOWER-RISK MYELODYSPLASTIC SYNDROMES RECEIVING LUSPATERCEPT IN CLINICAL PRACTICE

Kashyap Patel*[1], Debanjana Chatterjee[2], Christina Hughes[2], Anupama Vasudevan[3], John Li[3], Lindsay Aton[3], Husain Qureshi[3], Brandon Wang[3], Brandy Snyder[2], Ali McBride[2], Derek Tang[2]

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Background:

Luspatercept is approved for the treatment of anemia in patients (pts) with lower-risk myelodysplastic syndromes (LR-MDS) with or without prior erythropoiesis-stimulating agent use and who may require regular red blood cell (RBC) transfusions. Luspatercept recommended starting dose is 1 mg/kg once every 3 weeks, with dose escalation to 1.33 and 1.75 mg/kg allowed for pts who are transfusion dependent (TD), where pts remain TD after ≥2 consecutive doses (6 weeks). However, real-world dose titration and subsequent clinical outcomes have not been well characterized in the literature.

Aims:

To evaluate the clinical benefit of luspatercept dose titration among pts with LR-MDS in US clinical practice who initiated luspatercept across all lines of therapy (LOTs).

Methods:

This study used electronic medical records from the Integra Precision Q de-identified database of >3 million community-based oncology pt records. Eligible pts were ≥18 years, diagnosed with LR-MDS (Revised International Prognostic Scoring System [IPSS-R] score of Very low, Low, or Intermediate risk; physician reported/calculated when values not available in pts' records) between Jan 1, 2016 and Jun 30, 2022 (with ≥2 MDS codes and ≥2 office visits), received luspatercept, had a first luspatercept dose escalation up to 1.33 mg/kg (which is not the maximum approved dose) and continued treatment for ≥8 weeks at the same escalated dose, and had follow-up data until Dec 31, 2022. Pts were considered non-TD (NTD)/transfusion independent (TI) if they received 0 RBC units, and TD if they received ≥1 RBC unit. TD was assessed separately from luspatercept treatment initiation to first dose escalation, or in the 8 weeks post dose escalation. Key clinical outcomes post luspatercept dose escalation were TI rates for ≥8 weeks in pts who were TD prior to dose escalation, and hemoglobin (Hb) level changes in pts who were NTD prior to dose escalation. Descriptive statistics were used to analyze pt characteristics and transfusion status (TD/NTD/TI), including Hb levels among pts who were NTD prior to dose escalation.

Results:

Of 350 pts receiving luspatercept, 328 (94%) had complete dose information and 236 (85%) had a dose escalation, of whom 127 (54%) across all LOTs continued the same escalated dose for ≥8 weeks and were included in this study. Mean age was 74.0 (SD ±7.8) years, 70 (55%) pts were men, and 120 (94%) were seen in community practices. Overall, 57 (45%) pts had MDS with ring sideroblasts, and 117 (92%), 9 (7%), and 1 (1%) had a Very Low, Low, or Intermediate IPSS-R score at diagnosis, respectively. Luspatercept was first LOT for 8 pts (6%), second for 90 (71%), and third for 29 (23%). Overall, 66 pts were TD, and 61 were NTD prior to dose escalation. Among pts who were TD, 31 (47%) achieved TI post dose escalation. Among pts who were NTD, the majority (n=50; 82%) maintained NTD status, and mean Hb levels numerically increased post dose escalation. Of the 11 NTD pts who became TD after dose escalation, all had received luspatercept as their second (n=8, 73%) or third (n=3, 27%) LOT. Most (70%) pts who were NTD prior to dose escalation had their first dose escalation >3 to ≤6 weeks (23%, n=14/61), >6 to ≤9 weeks (18%, n=11/61), or >21 weeks (30%, n=18/61) after luspatercept initiation.

Summary/Conclusion:

Appropriate dose escalation of luspatercept in clinical practice may help to achieve TI among pts with LR-MDS who are TD. For pts who are NTD, dose escalation of luspatercept may help maintain NTD and contribute to increased Hb levels.

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PAPER: REAL-WORLD DOSE ESCALATION AND OUTCOMES AMONG PATIENTS WITH LOWER-RISK MYELODYSPLASTIC SYNDROMES RECEIVING LUSPATERCEPT IN CLINICAL PRACTICE

3 QUANTIFYING THE RELATIONSHIP BETWEEN TRANSFUSION INDEPENDENCE AND OVERALL SURVIVAL IN LOWER-RISK MYELODYSPLASTIC SYNDROMES

Luca Malcovati*[1, 2], Rena Buckstein[3], Mrudula B. Glassberg[4], Steve Kanters[5], Sean P. Harrigan[5], Sven Klijn[6], Barkha Aggarwal[4], Siguroli Teitsson[7], Aylin Yucel[6]

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Background:

Many pharmaceutical agents for the treatment of lower-risk myelodysplastic syndromes (LR-MDS), such as the novel erythroid maturation agent luspatercept, aim to reduce MDS-related anemia and improve red blood cell transfusion independence (RBC-TI). Through improved health, improvements in overall survival (OS), the gold-standard clinical outcome, may be expected. Although some studies have shown an association between RBC-TI and OS, none have explored the impact of RBC-TI acquired through treatment nor the association to varying definitions of RBC-TI.

Aims:

To explore and quantify the association between RBC-TI (and related intermediate outcomes) and OS since treatment initiation among treated patients with transfusion-dependent (TD) LR-MDS.

Methods:

We conducted individual patient data meta-analyses using 6 clinical trials among patients with RBC-TD LR-MDS: 3 luspatercept trials (COMMANDS [NCT03682536], MEDALIST [NCT02631070], and PACE [NCT01749514 and NCT02268383]) and 3 lenalidomide trials (5013-MDS-003 [NCT00065156], -004 [NCT00179621], and -005 [NCT01029262]). The analysis consisted of risk prediction modeling to estimate the impact of intermediate transfusion related endpoints on OS while controlling for potential confounders. Each varying definition of RBC-TI and adjacent endpoints were investigated individually, and achievement of ≥ 12 weeks RBC-TI in the first 24 weeks of treatment served as the primary intermediate endpoint. Variable selection was conducted using both LASSO Cox regression and clinical input, with the selected variables being: baseline age, sex, body mass index, Eastern Cooperative Oncology Group performance status (ECOG PS), International Prognostic Scoring System-Revised (IPSS-R) score, ring sideroblasts, time since diagnosis, prior erythropoiesis-stimulating agent treatment, platelet level, serum ferritin level, and serum erythropoietin level. Cox proportional hazards regression, with mixed-effects and immortal time bias adjustments, was used to conduct the predictive modeling. Data were split into training and testing sets (75%–25% split), with the testing set used for model validation. Model performance was assessed using time-dependent area under the curve (AUC) for 1 through 5 years.

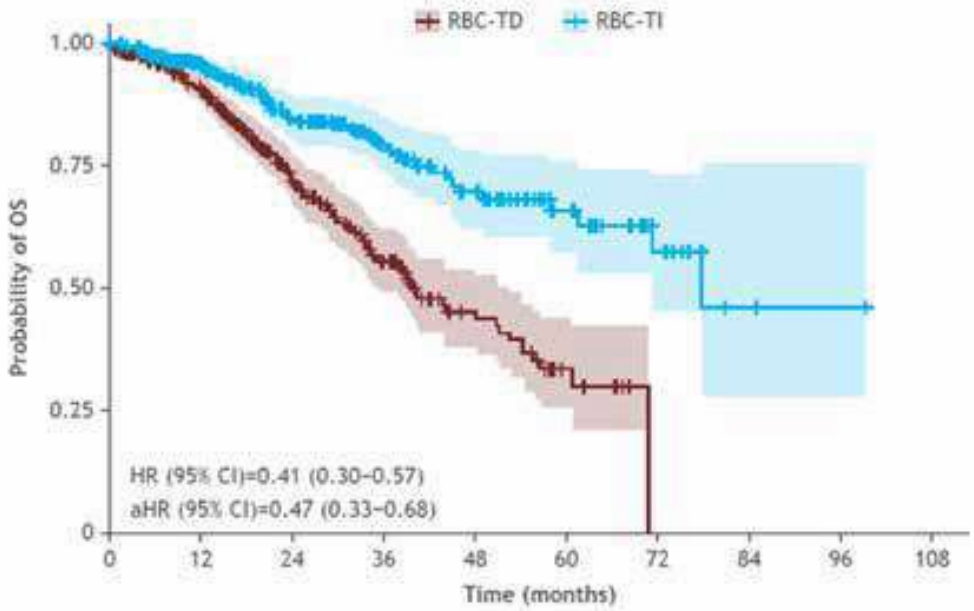
Results:

The cohort included 1136 patients across the 6 trials. The median age was 72.0 years (interquartile range [IQR], 65.0–78.0), while the median follow-up time was 25.5 months (IQR, 8.1–54.5). Results of the analysis for 12-week RBC-TI are summarized in the Figure. The adjusted hazard ratio (aHR) for OS among patients achieving RBC-TI relative to those maintaining RBC-TD was 0.47 (95% confidence interval [CI], 0.33–0.68). Among all variables included in the model, RBC TI demonstrated the strongest effect. Moreover, differences in survival probabilities between patients achieving RBC-TI and those maintaining RBC-TD persisted over time. Specifically, the 5-year survival was 66% (95% CI, 57–76) for RBC-TI patients compared with 34% (95% CI, 26–44) among RBC-TD patients. The model was deemed both valid (using the testing set) and useful. To this end, the time-varying AUC scores ranged from 0.66 to 0.87 suggesting that the model has acceptable-to-high predictive capability. Analyses using other definitions of transfusion endpoints led to models with similar predictive abilities and HRs.

Summary/Conclusion:

Our study highlights the association and strong predictive power of RBC-TI outcomes for OS. Despite RBC-TI being evaluated within the initial 24 weeks of treatment, it informs 5-year survival among patients with TD LR-MDS.

Figure. Kaplan-Meier curve
≥ 12 weeks of RBC-TI in the first 24 weeks since treatment initiation



No. at risk

RBC-TD	396	287	164	81	32	9	0	0	0	0
RBC-TI	340	243	156	84	51	24	11	3	2	0

Kaplan-Meier curve for training set (75% of data).
aHR, adjusted hazard ratio; OS, overall survival; RBC, red blood cell; TD, transfusion dependent; TI, transfusion independent.

Read more:

PAPER: QUANTIFYING THE RELATIONSHIP BETWEEN TRANSFUSION INDEPENDENCE AND OVERALL SURVIVAL IN LOWER-RISK MYELODYSPLASTIC SYNDROMES

4 CLINICAL BENEFIT OF LUSPATERCEPT IN TRANSFUSION-DEPENDENT, ERYTHROPOIESIS-STIMULATING AGENT-NAIVE PATIENTS WITH VERY LOW-, LOW- OR INTERMEDIATE-RISK MYELODYSPLASTIC SYNDROMES IN THE COMMANDS TRIAL

Valeria Santini*[1], Amer M. Zeidan[2], Uwe Platzbecker[3], Matteo Giovanni Della Porta[4, 5], Guillermo Garcia-Manero[6], Jiahui Li[7], Sandra Kreitz[8], Veronika Pozharskaya[7], Shelonitda Rose[7], Yinzhi Lai[7], Barkha Aggarwal[7], David Valcárcel[9], Pierre Fenaux[10], Jake Shortt[11], Rami S. Komrokji[12]

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Background:

There is an unmet need for an effective treatment (tx) that provides durable benefit for patients (pts) with anemia due to lower-risk myelodysplastic syndromes (LR-MDS).

Aims:

To report clinically meaningful responses to luspatercept tx in transfusion-dependent (TD), erythropoiesis-stimulating agent (ESA)-naive pts with LRMDS in the COMMANDS trial (NCT03682536).

Methods:

Eligible pts were ≥ 18 years of age, had LR-MDS with or without ring sideroblasts and < 5% bone marrow blasts, endogenous serum erythropoietin < 500 U/L, required red blood cell (RBC) transfusions (defined as 2–6 RBC units/8 weeks [wk] for ≥ 8 wk prior to randomization), and were ESAnaive. Pts were randomized 1:1 to subcutaneous administration of luspatercept (1.0–1.75 mg/kg) once every 3 wk or epoetin alfa (450–1050 IU/kg) once weekly for ≥ 24 wk. New assessments of clinical benefit reported here include achievement and duration of ≥ 50% reduction in RBC units transfused over ≥ 12 wk and ≥ 24 wk (wk 1–end of tx [EOT]), transfusion burden (TB) on tx (wk 1–24), time to first transfusion, achievement and cumulative duration of all separate RBC transfusion independence (RBC-TI) ≥ 12 wk response episodes (wk 1–EOT), and mean hemoglobin (Hb) increase ≥ 1.5 g/dL over wk 1–24.

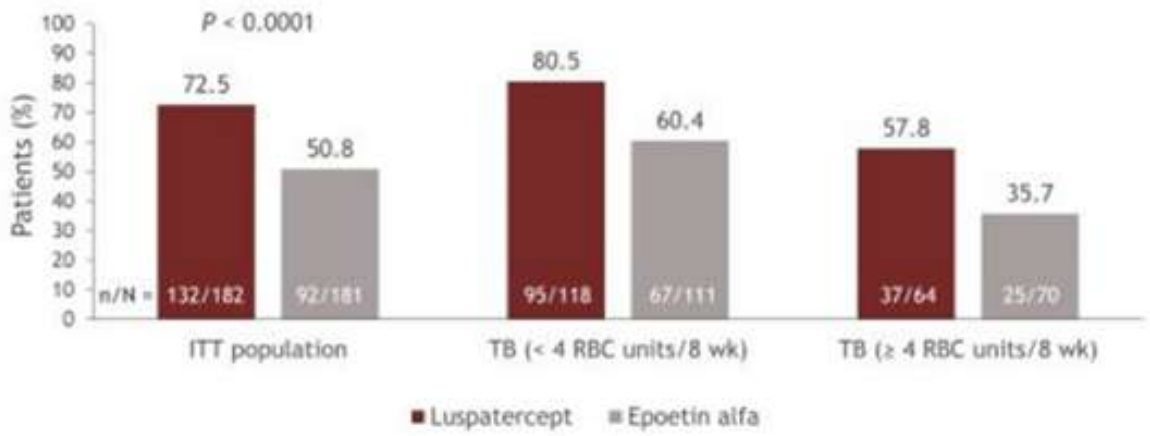
Results:

As of March 31, 2023, 151/182 (83.0%) pts treated with luspatercept and 121/181 (66.9%) pts treated with epoetin alfa achieved ≥ 50% reduction in RBC units transfused over ≥ 12 wk (wk 1–EOT; P = 0.0002), with median (95% confidence interval [CI]) durations of 130.0 (120.6–not evaluable [NE]) and 77.0 (54.9–123.1) wk, respectively (P = 0.0004). A greater proportion of luspatercept versus epoetin alfa pts achieved ≥ 50% reduction in RBC units transfused over ≥ 12 wk (wk 1 EOT), regardless of baseline (BL) TB: 105/118 (89.0%) pts treated with luspatercept versus 82/111 (73.9%) pts treated with epoetin alfa with BL TB < 4 RBC units/8 wk and 46/64 (71.9%) pts receiving luspatercept versus 39/70 (55.7%) pts receiving epoetin alfa with TB ≥ 4 RBC units/8 wk. Similarly, achievement of ≥ 50% reduction in RBC units transfused over ≥ 24 wk (wk 1–EOT) favored luspatercept over epoetin alfa (P < 0.0001; Figure), with median (95% CI) duration of 160.0 (135.0 - NE) wk in the luspatercept arm and 117.4 (80.1–NE) wk in the epoetin alfa arm (P = 0.0011). The median (interquartile range) number of RBC units transfused during wk 1–24 of tx was 1.0 (0–5.0) in the luspatercept arm and 3.0 (0–8.0) in the epoetin alfa arm. The median (95% CI) time to first transfusion was 155.0 (80.0–266.0) days for luspatercept versus 42.0 (23.0–55.0) days for epoetin alfa pts (P < 0.0001). Among pts who achieved RBC-TI ≥ 12 wk (wk 1–24), 22/124 (17.7%) luspatercept pts versus 12/88 (13.6%) epoetin alfa pts achieved ≥ 2 separate RBC-TI ≥ 12 wk response episodes (ie, achieved RBC-TI ≥ 12 wk response, lost RBC-TI response, then later achieved RBC-TI again) during the entire tx period. The cumulative median (95% CI) duration of all response episodes (wk 1–EOT) was 147.9 (122.0–NE) wk in the luspatercept arm and 95.1 (73.1–NE) wk in the epoetin alfa arm (P = 0.0067). Mean Hb increase ≥ 1.5 g/dL over wk 1–24 was achieved by 135/182 (74.2%) luspatercept pts and 95/181 (52.5%) epoetin alfa pts (P < 0.0001).

Summary/Conclusion:

Significantly greater proportions of pts treated with luspatercept than with epoetin alfa achieved improvements in Hb levels, reduction in TB and RBC units transfused, and had durable RBC-TI responses. Luspatercept provided clinically meaningful outcomes, supporting its use as the preferred tx for ESA-naive pts with LR-MDS-associated anemia.

Figure. Achievement of ≥ 50% reduction in RBC units transfused over ≥ 24 wk (wk 1-EOT)



EOT, end of treatment; ITT, intent to treat; RBC, red blood cell; TB, transfusion burden; wk, week.

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PAPER: CLINICAL BENEFIT OF LUSPATERCEPT IN TRANSFUSION-DEPENDENT, ERYTHROPOIESIS-STIMULATING AGENT-NAIVE PATIENTS WITH VERY LOW-, LOW- OR INTERMEDIATE-RISK MYELODYSPLASTIC SYNDROMES IN THE COMMANDS TRIAL

5 CLINICAL EXPERIENCE WITH LUSPATERCEPT THERAPY IN LOW-RISK MYELODYSPLASTIC SYNDROMES WITH TRANSFUSION DEPENDENCY, POSITIVE EFFECT OF COMBINATION THERAPY WITH ERYTHROPOIETIN

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Background:

Luspatercept, an inhibitor of the TGF-beta pathway, represents a new option for anemic patients with lower-risk myelodysplastic syndromes (MDS) with transfusion dependence (TD) who do not respond to erythropoiesis stimulating agents (ESA) therapy or are not suitable candidates for this treatment. We present real-life experience with luspatercept therapy from 2 hematology centers in the Czech Republic.

Aims:

To analyze real live data of luspatercept therapy in MDS

Methods:

From January 2019 to January 2024, 54 MDS patients (pts) (M/F - 33/21) with median age 74 (range 55-95) were treated with luspatercept ± ESA at two Charles University hematology centers in Prague and Hradec Kralove. WHO 2016 classication was: MDS-RS-MLD 32, MDS-MLD 7, 2 pts with 5q- + ring sideroblasts (RS). RS, MDS/MPN: 12 RARS-T, and 1patient with CMML-0 +RS. Information about SF3B1 mutation was available in 45 pts. IPSS-R categories were: 6 very low, 42 low, 6 intermediate pts (we did not treat high or very high-risk patients). In IPSS-M (molecular) (35 pts evaluated) were: very low + low15, moderate low 9, moderate high 7, high 4, very high 0 pts. Median follow-up was 17 months (range 1-54). All pts were TD. Thirty-five (64,8%) pts belonged to a high transfusion burden group (HTB) with ≥4 transfusion units (TU)/8 weeks, 35,2% to a LTB group (<4TU/8 weeks). The median time between diagnosis and initiation of luspatercept was 27 months (range 4-156). ESA were used prior luspatercept in 45 pts. Luspatercept as a rst line treatment was only in 9 pts.One third of pts had several previous lines of therapy. Thirty-three (61%) pts were treated simultaneously with ESA.

Results:

Only pts who received luspatercept for ^{3}8 weeks (51 pts) were assessed by IWG criteria 2006. We evaluated the achievement of TI lasting 8,12,16 and 24 weeks during 48 weeks. Thirty-two (62,7 %) pts reached TI during the luspatercept treatment lasting ^{3}8weekes, 31(60,7) ^{3}12 weeks, 29 (56,8%) ^{3} 16 weeks and finally 25 (49%) pts reached TI lasting ^{3} 24 weeks. Only hematological improvement (HI) without TI was achieved in 6 pts (11.7%). Overall, however, HI +TI was achieved in 38 pts (74.5%). In 21(41%) pts, concomitant therapy with ESA led to improved response, 16 of whom reached TI. There were 13 (25,4%) non-responders. Eight (21%) patients experienced therapy failure and became again TD. To achieve an optimal response, we had to gradually increase the dose of luspatercept to 1.75 mg/kg in up to 35 pts with 23 responders (TI+HI). Median duration of response was 12 months (range 5-26). Therapy was discontinued in 14 pts: 5 due to progression of MDS, 6 due to death from other causes, 2 due to newly diagnosed non-hematological malignancy, one due to non compliance.* There were differences in the response according to transfusion burden: in LTB pts 77% and in HTB 53% reached TI. In low, very low IPSS-M group 86% pts responded (TI+ HI) and in moderate low group 62%. Seventy-seven percent RS+ reached TI + HI, from small RS- group only 1/7 pts reached TI. Among 39 SF3B1 positive pts 74,3% responded (TI+HI) with 61,5% TI. Luspatercept was very well tolerated without any adverse event higher then Gr II toxicity.

Summary/Conclusion:

We have demonstrated in real life clinical practice that luspatercept is a very effective agent, even in an unselected pretreated significantly TD MDS population. The effect was particularly high in the IPSS-M low and very low group. We believe that the relatively high response rate in our pts was influenced by the frequent use of a higher dose (1.75mg/kg) and especially by adding ESA to luspatercept in poorly responding patients.

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