Real-World Outcomes and Predictors of Response and Progression in Lower-Risk MDS Patients Treated With Luspatercept: A Single-Center Experience

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Introduction

Luspatercept is an erythroid maturation agent approved for the treatment of anemia in patients with lower-risk myelodysplastic syndromes (LR-MDS). While clinical trials have demonstrated its efficacy in reducing transfusion burden and inducing transfusion independence, real-world data remain limited, and predictors of both response and disease progression are still under investigation.

Aim and Methods

We retrospectively analyzed 46 LR-MDS patients (78.3% male; median age 76 years) treated at the MDS Unit - Careggi Hospital. Baseline variables (Table-1) included red blood cell transfusion burden (RBC-TB), IPSS-R, IPSS-M, cytogenetic risk and mutational status (t-NGS panel). *SF3B1* mutation was present in 82.6% of patients and 37 were classified as MDS-*SF3B1* or MDS-LB-RS per WHO 2022 criteria. RBC-TB and erythroid response were defined according IWG 2018 criteria. Associations were assessed via chi-square and non-parametric tests. Outcomes included response rates, disease progression, time to response, post-luspatercept treatments, and overall survival (OS).

		MDS unit Careggi Hospital (n=46)
Baseline characteristics	Age (median)	76 (65-78)
	Gender (male)	78.3 (36)
	Hgb (mean) g/dl	8.2 (7.8-8.7)
	Platelets (mean) x10^9/L	246 (185-306)
	ANC (mean) x10^9/L	2.3 (1.59-3.48)
	AMC (mean) x10^9/L	0.44 (0.26-0.68)
	Serum erythropoietin level (median) U/L	82.7 (n=41)
		% (n)
M-IPSS (n=41)	Very Low	4.9 (2)
	Low	51.2 (21)
	Moderate Low	19.5 (8)
	Moderate High	17.1 (7)
	High	4.9 (2)
	Very High	2.4 (1)
	Missing	5
R-IPSS (n=45)	Very low	4.4 (2)
	Low	68.9 (31)
	Intermediate	26.7 (12)
	Missing	1
RBC transfusion Burden (n=45)	NTD	15.5 (7)
	LTB	26.7 (12)
	HTB	57.8 (26)
Prior ESA treatment		89.1 (41)
Somatic mutations (n=44)	*SF3B1*	86.4 (38)
	SRSF2	15.9 (7)
	U2AF1	0 (0)
	ZRSR2	6.8 (3)
	TET-2	40.9 (19)
	DNMT3A	22.7 (10)
	ASXL-1	22.7 (10)
	TP53	6.8 (3)
	EZH-2	4.5 (2)
	IDH1	4.5 (2)
	IDH2	4.5 (2)
	SH2B3	6.8 (3)
	PHF6	2.3 (1)
	RUNX-1	0.9 (4)
	CBL	4.5 (2)
	JAK-2	18.2 (8)
WHO 2022 (n=46)	MDS-SF3B1 (or RS)	80.4 (37)
	MDS-LB	6.5 (3)
	MDS-IB1	2.2 (1)
	CMML	2.2 (1)
	MDS-SF3B1-T	8.7 (4)

Table 1: Characteristics of patients

Demographic and clinical features are reported; diagnosis according to WHO 2022 classification, somatic mutations, prognostic score according to IPSS revised and molecular IPSS.
NTD, non-transfusion dependent (0-3 units in 16 weeks prior luspatercept; LTB, low transfusion burden (4-7 units/16 weeks); HTB, high transfusion burden (≥ 8 units/16 weeks)

Results

Overall response was achieved in 45.6% of patients (19% obtained transfusion independence and 66.7% obtained ≥1.5 g/dL Hb increase), with a median time to response of 88 days (Table-2). Response was significantly associated with baseline RBC-TB (p=0.0139), but not with IPSS-R (p=0.683), IPSS-M (p=0.462), cytogenetic risk (p=0.179), or mutation burden (p=0.751). A trend toward higher IPSS-M scores was observed in patients who progressed (p=0.0848), despite IPSS-M categories were not significantly associated with progression (p=0.2637). Notably, 8 patients experienced disease evolution: 3 to AML, 2 to MDS-IB2, 1 to MDS-IB1, 1 to MDS/MPN-U, and 1 to systemic mastocytosis. Importantly, none of the patients achieving a complete erythroid response (≥1.5 g/dL Hb increase) progressed (p=0.0157), whereas progression occurred in 2 patients who obtained transfusion independence. RBC-TB increased from a median of 8 to 16 units/16 weeks post-treatment. Median OS was 523 days from treatment start (IQR: 279–930) and 232 days from treatment discontinuation. Subsequent therapies included best supportive care (n=14), HMA ± venetoclax (n=3), danazol (n=2), and investigational agents (n=2).

% (n)	MDS unit Careggi Hospital (n=46)
Overall response	45.6 (21)
Hgb increase more than 1.5 g/dl in NTD or Hgb increase more than 1.5 g/dl with RBC-TI in RBC-TD	66.7 (14/21)
RBC-TI without Hgb 1.5 g/dl increase	19 (4/21)
>50% reduction in RBC-TB	14.3 (3/21)
Response in NTD: Hgb increase more than 1.5 g/dl	85.7 (6/7)
Response in LTB	41.7 (5/12)
Hgb increase more than 1.5 g/dl and RBC-TI	16.7 (2/12)
RBC-TI without Hgb 1.5 g/dl increase	25 (3/12)
Response in HTB	34.6 (9/26)
Hgb increase more than 1.5 g/dl and RBC-TI	19.2 (5/26)
RBC-TI without Hgb 1.5 g/dl increase	3.8 (1/26)
>50% reduction in RBC-TB	11.5 (3/26)

Table-2: Different types of response according to transfusion burden

Discussion

Luspatercept showed favorable efficacy in LR-MDS in a real-world setting. Baseline RBC-TB emerged as a reliable predictor of response. However, predictors of progression remain undefined. Further research is needed to elucidate biomarkers and guide post-luspatercept strategies.

References

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