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Activity of Luspatercept and Erythroid-Stimulating Agents (ESAs) Combined for Treatment of Anemia in Lower-Risk Myelodysplastic Syndromes

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INTRODUCTION

- Luspatercept, a TGF-B fusion trap protein, is a first in class erythroid maturating agent approved by FDA for treatment of red blood cell transfusion dependent (RBC-TD) lower risk myelodysplastic syndromes (LR-MDS) with ring sideroblasts (RS).
- Erythroid stimulating agents (ESA) promote early stages of erythropoiesis while Luspatercept enhances terminal erythroid maturation..

AIM

- We report data on the activity of combining Luspatercept with ESA

METHOD

- We treated a cohort of pts off-protocol at Moffitt Cancer Center with ESA and Luspatercept combined if no response/loss of response was observed to Luspatercept monotherapy as add back strategy or upfront combination.
- Baseline RBC transfusion burden (TB) was defined as: non-transfusion dependent (NTD) (0 units in 8 weeks prior luspatercept), low TB (LTB) (1-5 units /8weeks) and high TB (HTB) (≥ 6 units /8 weeks).
- A hematological response (HI) was defined as (1) an objective Hgb increase of > 1.5 g/dl in NTD, (2) RBC-TI with Hgb increase of 1.5 g/dl, or RBC-TI without Hgb 1.5 g/dl increase or >50% reduction in RBC transfusion burden among RBC-TD.
- Luspatercept dose escalation and choice of ESA/dosing was at the discretion of the treating physician.

RESULTS

- Twenty-eight pts were treated with luspatercept and ESA combination after no response (**1º** failure) (n=18) or loss of initial response to luspatercept monotherapy (2º failure) (n=7) or as initial combination treatment (n=3).
- The median age was 72 years and 53.5% had MDS-RS subtype.
- Intermediate or lower risk MDS by IPSS-R in 96.4% of pts
- *SF3B1* somatic mutation was detected in 85.7%.
- The mean Hgb level was 8 g/dl and 43% were RBC HTB transfusion dependent
- The median serum erythropoietin (epo) level available for 18 pts at time of referral was 119.5 U/L.
- The majority had prior ESA treatment 89% (25) with 21.4% (6/25) hematological response to prior ESA monotherapy.
- Twelve pts (43%) had prior HMA and 11 pts (39%) had prior lenalidomide (Len) treatment.
- The majority of pts (27/28; 96%) had luspatercept dose escalation whereby 23 pts received 1.33 mg/kg, 25 pts received 1.75 mg, and only 1 pt did not receive any luspatercept dose escalation.
- The overall HI rate to luspatercept combined with ESA was 36% (10/28).
- HI according to baseline RBC-TB were observed in 33% (1/3) NTD, 56% (6/13) LTB and 33% HTB (4/12) pts respectively, p=.75.
- Five out 7 pts (71%) who responded originally to luspatercept alone (2º failure) responded to ESA add on whereas only 3 out of 18 pts (17%) who did not respond to luspatercept monotherapy (**1º** failure) responded when ESA was added.
- With upfront ESA + luspatercept combination, 2 out 3 pts responded.
- Among responders, the median duration of response from time of response to luspatercept monotherapy or combination was 18.9 months (5.4-27.3).
- As of last follow up, 15 pts (54%) discontinued treatment.
- Reason of discontinuation was lack of response in 12 pts and loss of response in 3 pts.
- No responses to combination ESA/luspatercept were observed among *SF3B1* wild type pts (n=4).
- No pts with serum epo > 500 u/l responded to addition of ESA, 25% of pts (2/8) with serum epo 200-500 u/l responded and 40% of pts (4/10) with serum epo less than 200 U/L responded.
- There was a trend of higher response among HMA and Len naïve pts.
- The HI rate was 25% (3/12) after HMA failure compared to 44% (7/16) in HMA naïve pts (p=.3). However, more pts post HMA failure were RBC-HTB 67% (8/12) compared to 25% (4/16) in HMA naïve, p=.05.
- The HI rate was 18% (2/11) for Len failure compared to 47% (8/17) Len naïve pts, (p=.1)

Baseline characteristics (n=28)	% (n)
Age (median)	72 (51-94)
Gender (male)	68(19)
Race (white)	96 (27)
MDS classification WHO 2016	
MDS-SLD	10.7 (3)
MDS-MLD	10.7 (3)
MDS-SLD-RS	32.1 (9)
MDS-MLD-RS	21.4 (6)
MDS del 5q	3.6 (1)
MDS/MPN-RS-T	21.4 (6)
R-IPSS	
Very low	21.4 (6)
Low	67.9 (19)
Intermediate	7.1 (2)
High	3.6 (1)
Hgb (mean) g/dl	8 (6.6-9.4)
Platelets (mean) x10^9/L	259 (16-814)
ANC (mean) x10^9/L	2.53 (.45-9.1)
Myeloblasts % (mean)	2 (0-4)
Serum erythropoietin level (median) U/L	119.5 (n=18)
RBC transfusion Burden	
NTD	11 (3)
LTB	46 (13)
HTB	43 (12)
Prior ESA treatment	89 (24)
Prior HMA treatment	42 (12)
Prior Lenalidomide treatment	39 (11)
Somatic mutations	
SF3B1	85.7 (24)
TET-2	44 (12/27)
DNMT3A	22 (6/27)
ASXL-1	4 (1/27)
TP53	4 (1/27)
JAK-2	12 (3/27)

Table-2 Response to combination Luspatercept and ESA	% (n)
Overall response (n=28)	36 (10)
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	18 (5/28)
RBC-TI without Hgb 1.5 g/dl increase	14 (4/28)
>50% reduction in RBC-TB	4 (1/28)
Response in NTD (n=3):Hgb increase more than 1.5 g/dl	33 (1/3)
Response in LTB (n=13)	38 (5/13)
Hgb increase more than 1.5 g/dl and RBC-TI	15 (2/13)
RBC-TI without Hgb 1.5 g/dl increase	23 (3/13)
>50% reduction in RBC-TB	0
Response in HTB (n=12)	33 (4/12)
Hgb increase more than 1.5 g/dl and RBC-TI	17 (2/12)
RBC-TI without Hgb 1.5 g/dl increase	8 (1/12)
>50% reduction in RBC-TB	8 (1/12)

CONCLUSION

- To our knowledge, this is the first proof of principle data confirming synergistic clinical activity combining luspatercept and ESA.
- Predictors of response included prior response to luspatercept monotherapy/frontline combination compared to primary luspatercept failure, endogenous serum epo levels < 500, *SF3B1* mutation, and being HMA/Len treatment naïve.