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Myelodysplastic Syndromes with Concomitant SF3B1 Mutation and Deletion of The Long Arm of Chromosome 5

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INTRODUCTION

- Both MDS-SF3B1 and isolated del(5q) MDS are recognized by WHO and ICC 2022 as unique molecularly defined MDS entities.
- Concomitant SF3B1 and del(5q) cases are classified as MDS del(5q).
- Reports including the molecular revised international prognostic scoring system (IPSS-M) indicates that concomitant SF3B1 mutation with del(5q) is associated with less favorable outcome. SF3B1del5q accounted for 7% of all SF3B1 cases in the IPSS-M cohort.
- Lenalidomide (len) is the treatment of choice for isolated del(5q) MDS and luspatercept (luspa) for MDS-SF3B1. There is scarce data about response of this entity to either len or luspa.

AIM

To assess the hematological response rate to current approved therapies including lenalidomide and luspatercept among lower risk (LR) MDS patients (pts) with SF3B1/del(5q).

METHOD

- This was a multicenter international retrospective analysis for patients diagnosed with concomitant del5q/SF3B1 MDS, with less than 5% myeloblasts, no complex karyotype who received at least one line of therapy.
- Hematological improvement (HI) was defined as hemoglobin (Hgb) increase 1.5 g/dl or more in non-transfusion dependent pts, or red blood cell transfusion independence among transfusion dependent pts.
- We identified two comparison cohorts, one with MDS-SF3B1 and one with isolated MDS-del5q to compare baseline characteristics and outcomes.

RESULTS

- We included 77 LR-MDS pts with isolated del(5q)/SF3B1. The median age at diagnosis was 70 years (30-87), 74% were females, 97% white and 13% classified as t-MDS. The median Hgb was 9.3 g/dl (5-13), median platelets 250 (32-1330) and median ANC 2.01 (1-11). The most common other concomitant somatic mutations were TP53 (26%), DNMT3A (23%) and TET-2 (21%). The median TP53 VAF was 16% (1-66%). R248W was most common hot spot (20%).
- The median overall survival (mOS) for the whole cohort was 66 months (mo) (95%CI 53-79). The mOS was 109 mo for TP53 WT compared to 64 mo for TP53 MT (p=0.22).
- 1st line therapy was Len for 46 pts (61%), erythroid stimulating agents (ESA) for 18 pts (23%), luspa for 4 pts (5%), hypomethylating agents (HMA) for 6 pts (8%) and other therapies for 2 pts (3%).
- Among 72 evaluable pts for response, the best HI rate to 1st line therapy was 53% (37 pts). The HI rate to Len, ESA, HMA and luspa was 64%, 42%, 20% and no response respectively as 1st line.
- 47 pts received 2nd line therapy, 12 (26%) Len, 4 (9%) Luspa, 22 (47%) HMA, 1 ESA, and 8 (17%) other treatments including clinical trials.
- Among 39 evaluable pts, the best HI rate to 2nd line therapy was 43% (17 Pts). The HI rate was 46% (5/11 pts), 50% (2/4 pts), 47% (8/17 pts) for Len, Luspa and HMA as 2nd line therapy respectively.
- 38 pts received ESA at any time, where among 33 pts evaluable for response, the HI rate was 27% (9pts). 60 pts received Len, at any time, and among 57 pts evaluable for response, the HI rate was 59%. There was no difference in response among TP53 WT 61% vs 50% for TP53 MT (p=.4). A total of 16 pts received Luspa at any time where HI rate was 18% (3pts). Finally, 37 pts received HMA at any time, among 32 responses evaluable HMA treated pts, the HI was 37% (12 pts)
- We compared the 77 MDS del5q/*SF3B1* cohort to 382 MDS-*SF3B1* pts and 133 MDS isolated del5q MDS pts. Outcome for del5q/*SF3B1* MDS pts was closer to del5q MDS and inferior to MDS-*SF3B1*.

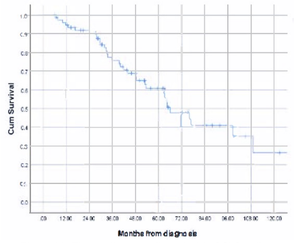


Figure 1A. The median overall survival (mOS) for all patients (n=77) was 66 months (95%CI 53-79).

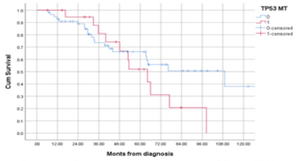


Figure 1B. The median overall survival (mOS) for TP53 mutated and wild type was 64 months and 109 months respectively. P=0.22

	Lenalidomide	Luspatercept	HMA	ESA
1st line treatment	61% (n=46)	5% (n=4)	8% (n=6)	23% (n=18)
HI to 1st line = 53% (n=37)	64%	0%	20%	42%
2nd line treatment (n=47%)	26% (n=12)	9% (n=4)	47% (n=22)	n=1
HI to 2nd line = 43% (n=17/39)	46% (n=5/11)	50% (n=2/4)	47% (n=8/17)	N/A
HI any time	59%	18%	37%	27%

Table1. Hematological response (HI) for patients receiving lenalidomide, luspatercept, hypomethylating agents (HMA) which might include either azacitidine, decitabine or oral HMA), or erythrocyte stimulating agents (ESA).

CONCLUSIONS

- In this largest retrospective cohort of SF3B1/del(5q) MDS pts we report mOS of 66 mo, which is better than IPSS-M cohort, however in contrary to IPSS-M, our analysis was limited to pts with less than 5% myeloblasts.
- The mOS of concomitant del5q/SF3B1 is still inferior to either isolated del5q or SF3B1 entities and maybe driven by high rate of concurrent TP53 MT observed.
- Response to Len was similar to isolated del5q whereas response to luspa was inferior to MDS-SF3B1 and more observed as 2nd line therapy.
- Our data suggests that Len should be 1st line therapy for those pts followed by luspa and HMA.

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