Abstract: P736

Title: ANALYSIS OF RESPONSE RATES AND OUTCOMES IN ERYTHROID-PREDOMINANT MYELODYSPLASTIC SYNDROMES (MDS) TREATED WITH VENETOCLAX-BASED REGIMENS

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Background:

The BCL-2 inhibitor venetoclax is an emerging therapeutic option in higher-risk myelodysplastic syndromes (MDS). Pre-clinical data have shown that erythroid-differentiated myeloid leukemias exhibit resistance to BCL-2 inhibitor therapy, likely mediated by reliance on alternative anti-apoptotic effectors such as BCL-XL (Kuusanmäki et al., *Blood* 2022). This may result in inferior outcomes with venetoclax-based regimens in erythroid-predominant (EP) MDS.

Aims:

We sought to establish the frequency, biological characteristics, and natural history of EP MDS. We then focused on evaluating the outcomes of patients with EP versus non-EP MDS when treated with venetoclax-based regimens.

Methods:

We first performed a retrospective analysis of a historical cohort (1996-2021) of unselected patients with newly diagnosed MDS to establish the frequency and characteristics of EP MDS. We then performed a focused chart-review study in a more contemporary cohort spanning 2015 to 2022 and included all patients with a WHO 2016 diagnosis of MDS treated with venetoclax-containing regimens. The EP subset was defined as patients with a bone marrow erythroid component (erythroblasts plus proerythroblasts) of 50% or greater. Responses were assessed as per IWG 2006. The Kaplan Meier method was used to estimate overall survival (OS) and event-free survival (EFS, with an event defined as going off therapy due to lack of efficacy, progression after achieving response, AML transformation, or death from any cause). The analysis was stratified by EP vs non-EP MDS.

Results:

In a cohort of 1126 patients with newly diagnosed MDS spanning 1996 to 2021 unselected for risk or therapy received, EP was identified in 165 (15%) patients. When compared with non-EP MDS, EP MDS was characterized by more frequent *TP53* mutations (43% vs 33%, p=0.033) and complex cytogenetics (40% vs 26%, p<0.001). OS was shorter in EP versus non-EP cases (median 21.3 versus 24.9 months, p=0.028).

In the contemporary cohort (2015-2022), we identified 108 patients with MDS (15 EP, 93 non-EP MDS) treated with venetoclax-based regimens. All patients were treated with venetoclax combined with an HMA backbone. 55/108 (51%) of the patients had prior hypomethylating agent (HMA) exposure. The median follow-up time was 16.6 months and the median number of cycles given was 3 (range 1-16).

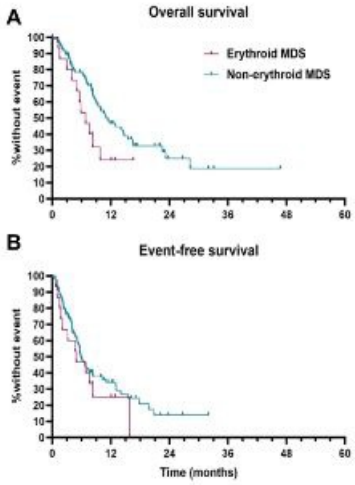
In the venetoclax plus HMA-treated cohort, the EP cases (n=15) were enriched for higher-risk disease by IPSS-R and *TP53* mutations compared to the non-EP cases (**table 1**). Both the overall response rate (ORR) and complete remission (CR) rate were similar between the EP and non-EP cases (ORR 67% vs 71% in EP vs non-EP, p=0.765; CR 20% vs 13% in EP vs non-EP, p=0.435). There was a trend towards shorter OS in the EP cases (median OS 6.8 months in EP vs 11.1 months in non-EP MDS, p=0.060, **figure panel A**). There was no significant difference in EFS between the EP and non-EP cases (median EFS 4.9 months in EP vs 5.9 months in non-EP MDS, p=0.335, **figure panel B**).

Summary/Conclusion:

Within the limitations of this retrospective and heterogeneous cohort, we observed a trend towards inferior OS, but not EFS, in EP MDS compared to non-EP MDS when treated with venetoclax-based regimens. This may be driven, at least in part, by more frequent high-risk disease and *TP53* mutations in EP MDS. Larger studies, ideally prospective, are needed to better understand the role of erythroid differentiation in venetoclax responsiveness in the clinical setting.

Table 1	EP-MDS (n=15)	Non-EP MDS (n=93)	p
Age	67 [53-84]	71 [47-94]	0.08
Prior chemo/ radiotherapy	5 (33)	21 (23)	0.37
Prior HMA exposure	7 (47)	48 (52)	0.72
Hemoglobin	8.4 [6.5-10.4]	8.5 [6.2-14.4]	0.22
Platelets	46 [16-146]	57 [6-567]	0.31
ANC	0.51 [0.06-1.8]	1.25 [0.00-26.1]	0.02
BM blast %	12 [5-16]	12 [2-19]	0.27
BM erythroid %	55 [50-81]	21 [0-46]	<0.01
IPSS-R			0.06
Very Low	0 (0)	1 (1)	
Low	0 (0)	0 (0)	
Intermediate	0 (0)	12 (13)	
High	2 (13)	34 (37)	
Very High	13 (87)	46 (49)	
***TP53*-mutated**	7 (47)	25 (27)	0.119

Data displayed as n(%) or median [range]



Keywords: Venetoclax, Myelodysplastic syndrome