3870 Prognostic and Predictive Impact of Small PNH Clones in a Large Cohort of Patients with Myelodysplastic Syndromes and Aplastic Anemia: A Single-Center Experience

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Hall GH (San Diego Convention Center)

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Background: the use of high sensitive FLAER in the last 10 years improved the detection of very small PNH clones (<1%) in various hematologic conditions, including aplastic anemia (AA)/myelodysplastic syndromes (MDS). Although generally considered unremarkable, the recent observation of asymptomatic end-organ damage due to undiagnosed thrombosis even in patients without overt hemolysis questions the assertion that small PNH clones are of subclinical value.

Aim: To evaluate the prevalence of PNH clones ≥0.01% in AA/MDS patients tested at a single tertiary center, and to assess their impact on disease prognosis (leukemic evolution, death), occurrence of thrombosis, and response to current therapies.

Methods: We retrospectively collected clinical (diagnosis, stage, therapy, complications and outcome) and laboratory features (complete blood counts, LDH, PNH clone size) of 869 MDS and 531 AA patients tested from March 1998 till October 2017.

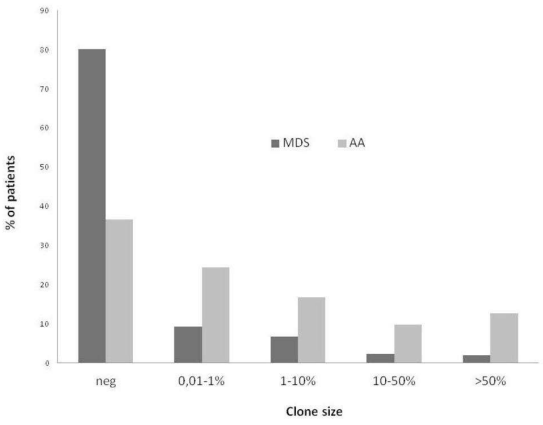
Results: Figure 1 shows clinical and laboratory characteristics of MDS and AA patients, divided according to the presence/absence of PNH clones. A PNH clone was less frequently found in MDS cases versus AA (20.3% vs 61%). Focusing on MDS, PNH+ cases were significantly more hypoplastic, mainly displayed IPSS low/int-1 score, and showed deeper cytopenias (significantly for Hb and PLT) and higher LDH levels. Dividing patients according to clone size (negative, 0.01-1%, 1.01-10%,10.01-50%, and >50% on granulocytes), we observed a significant worsening of cytopenia and raise of LDH along with clone size increase. Likewise, lower IPSS risk patients more frequently displayed a greater clone size. As regards therapy, PNH+MDS showed significantly higher response rates to immunosuppressive therapies (ATG and CyA, 84% vs 44.7%, p=0.01) and to HSCT (71% vs 56.6%, p=0.09) compared to PNH-, and the cumulative probability of response to any treatment significantly improved

along with clone size increase (from 52 to 100%, p=0.03). In addition, PNH+MDS showed lower rate of progression and AML evolution, and a longer OS [mean 11.9+0.7 years (10.5-13.3) vs 7.3+0.3 (6.6-7.9), p<0.0001] compared to PNH- ones. Interestingly, we observed a significant reduction of death frequency along with clone size increase (56% in PNH- vs 24% in PNH+ with clone size 0.01-1%, p<0.0001). However, PNH+MDS had a higher incidence of thrombotic events, with greater frequency along with clone size increase (from 5% in PNH- to 50% in PNH+ with clone size >50%, p<0.0001). As expected, worse OS also significantly correlated with older age, male gender, transfusion dependence, MDS progression/AML evolution, higher IPSS score, and non-response to therapy.

Regarding AA, together with a higher frequency of PNH clones, we also found a higher frequency of large clones (>10%) compared to MDS (p=0.04, bars chart). PNH+AA showed deeper thrombocytopenia, higher reticulocyte counts and LDH values. As observed for MDS, we found a significant worsening of cytopenia and raise of LDH along with clone size increase. In addition, PNH+ AA showed higher response rates compared to PNH- (97 vs 77% for HSCT, p=0.01; 78 vs 50% for IST, p<0.0001; and 88% vs 65% considering any treatment, p<0.0001). PNH+AA also showed lower rate of MDS progression and death (p=0.01 and p<0.0001), and longer OS [mean 15.8+0.43 years (14.9-16.7) vs 6.5+0.35 (5.8-7.21), p<0.0001]. Also in AA, we observed a significant reduction of death frequency along with clone size increase (32.1% in PNH- vs 9.2% in PNH+ with clone size 0.01-1%, p<0.0001). Worse OS also correlated with older age, male gender, presence of cytopenia, and non-response to therapy.

Conclusions: Prevalence of PNH clones of any size is high in patients with MDS and AA. We firstly show a positive impact of PNH clone positivity on response to IST and HSCT in MDS. The presence of a PNH clone also correlated with lower disease progression and better OS. Furthermore, we confirm the known favourable prognostic and predictive value of PNH clones in a large AA cohort. Clone size analysis suggests that even small clones (0.01-1%) have a clinical and prognostic significance.

	MDS		p	AA		p
	PNH- N=693	**PNH+ N=176**		**PNH- N=204**	**PNH+ N=327**	
Males	424 (61.2)	91 (51.7)	0.02	107 (52.5)	167 (51.1)	NS
Females	269 (38.7)	85 (48.3)	0.02	97 (47.5)	160 (48.9)	NS
Median age years	63 (11-92)	59 (19-89)	<0.00004	46 (6-91)	43 (9-7)	NS
Hematologic values	**N=693**	**N=176**		**N=204**	**N=327**	
Anemia (Hb<10) N(%)	258 (37.2)	81 (46)	0.04	107 (52.5)	158 (48.3)	NS
Thrombocytopenia (PLT<100) N(%)	272 (39.2)	106 (60.2)	<0.0001	6 (2.9)	241 (73.7)	<0.0001
Neutropenia (ANC<1500) (N%)	320 (46.17)	94 (53.4)	NS	121 (59.3)	198 (60.5)	NS
Median LDH U/L	193 (73-1864)	233 (133-1520)	<0.00001	187 (78-748)	223 (70-3102)	<0.00001
monosomy 7 N(%)	28 (4)	14 (7.5)	0.04	5 (2.5)	8 (2.4)	NS
complex karyotype N(%)	44 (6.3)	6 (3.2)	NS	-	-	-
Treated patients N(%)	**365 (52.6%)**	**108 (61.3%)**		**161 (78.9)**	**323 (98.8)**	
Chemotherapy N(%)	191 (52)	29 (27)	<0.0001	-	-	-
CSA N(%)	40 (11)	37 (34)	0.0001	97 (60)	273 (84)	<0.0001
ATG N(%)	10 (3)	13 (12)	0.0002	72 (45)	245 (76)	<0.0001
Androgen N(%)	-	-	-	10 (6)	3 (0.9)	0.002
Azacytidine N(%)	123 (34)	19 (18)	0.002	-	-	-
Eltrombopag N(%)	8 (2)	5 (5)	NS	11 (6.8)	23 (7.1)	NS
HSCT N(%)	141 (39)	40 (37)	NS	55 (34)	82 (25)	0.05
Eculizumab N(%)	0 (0)	7 (6)	<0.0001	0 (0)	48 (14.8)	<0.0001
Outcome	**N=693**	**N=176**		**N=204**	**N=327**	
MDS Progression N(%)	34 (4.9)	1 (0.6)	0.003	14 (6.9)	7 (2.1)	0.01
AML evolution N(%)	88 (12.7)	12 (6.8)	0.01	6 (2.9)	6 (1.8)	NS
Thrombosis N(%)	37 (5.3)	16 (9)	0.05	11 (5.4)	21 (6.4)	NS
Death N(%)	308 (44.4)	48 (27.3)	<0.0001	70 (34.3)	38 (11.6)	<0.0001
MDS type and IPSS risk	**N=693**	**N=176**				
RCMD/RCUD N(%)	271 (39)	55 (31.3)	NS			
RA N(%)	28 (4)	4 (2.3)	NS			
RA del5q N(%)	23 (3.3)	3 (1.7)	NS			
HypoMDS N(%)	90 (13)	67 (38.1)	<0.0001			
RAEB1/2 N(%)	199 (28.7)	36 (20.5)	0.03			
RARS/RARS-T	34 (4.9)	3 (1.7)	NS			
Other MDS-F N(%)	41 (5.9)	8 (4.60)	NS			
IPSS low N(%)	281 (40.6)	59 (33.5)	NS			
IPSS int1 N(%)	237 (34.2)	85 (48.3)	<0.0001			
IPSS int2 N(%)	147 (21.2)	22 (12.5)	0.01			
IPSS high N(%)	28 (4)	10 (5.7)	NS			



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