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ORAL ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Clinical and Prognostic Implications of *WT1* Mutations in De Novo and Relapsed Acute Myeloid Leukemia

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Introduction

Wilms Tumor 1 (*WT1*) is integral to cell proliferation and survival and is mutated in up to 10-15% of patients (pts) with acute myeloid leukemia (AML). *WT1* mutated (*WT1* ^{m}) AML frequently co-occurs with fms-like tyrosine kinase 3 (*FLT3*) and nucleophosmin 1 (*NPM1*) mutations, and is generally thought to impart poorer outcomes, however the impact of *WT1* ^{m} remains incompletely understood.

Methods

We analyzed 307 pts with *WT1* ^{m} AML, identified through next generation sequencing panels of recurrently mutated myeloid genes performed at two large academic cancer centers between 2015 - 2022. Of the 307 pts, 161 (52%) had *WT1* ^{m} at AML diagnosis (ND) and 146 (48%) were identified at relapse (RR). Here we describe the baseline characteristics and outcomes in pts with *WT1* ^{m} AML with emphasis on co-mutated *FLT3* and *NPM1*.

Results

In pts with ND *WT1* ^{m} AML, the median age was 59 years (range,22-87). Pts most commonly had intermediate (41%) or adverse (43%) risk disease by ELN 2022 criteria. 51% (n=82) had co-mutated *FLT3* (ITD or TKD). Among pts with *FLT3* mutated AML, 30% (37%) also had co-mutated *NPM1*. 10 (7%) pts had co-mutant *NPM1* ^{m} without *FLT3* ^{m}. Median OS in the ND cohort was 19.8 months. Variant allele frequency (VAF) ranges of *WT1* ^{m} were 1-98 (median 27) and 1-97 (median 13) in the ND and RR cohorts respectively. OS was affected by mutational profile (table 1) with triple mutated *NPM1/FLT3/WT1* exhibiting worse OS compared to others. 68% of ND pts received intensive chemotherapy (+/- venetoclax (VEN)) at time of diagnosis with mOS of 26.5 mos vs. 11.1 mos (p = <0.0001) for pts treated with lower intensity therapy (+/- VEN).

Improved OS was observed in pts with ELN2022 favorable risk disease (mOS not reached (NR)) and in pts receiving an allogeneic hematopoietic stem cell transplant (SCT). Pts with ND AML and ELN2022 intermediate-risk disease who underwent SCT had significantly longer OS of 47.9 mos vs. 11.8 mos (p<0.0001, figure 1). In the ND cohort, pts had significantly improved OS if they underwent SCT after achievement of CR1 compared to SCT after first relapse, mOS NR vs. 38 months (p=0.00039),

respectively. Notably, the median age of pts who received SCT was 50 (22-74) with 16% having secondary (s-AML) or therapy related (t-AML). Of those who did not undergo SCT median age was 63 (23-87) and had with 28% of pts with (s- or t-AML).
Within the RR cohort, 44 (30%) pts acquired *WT1* mutation post SCT. 56 (38%) were *FLT3* ^{m} (25 pts with co-mutated *NPM1)* and 10 (7%) *NPM1* ^{m} mutated (without *FLT3* ^{m}*)*. The mOS in the RR cohort (from time of *WT1* ^{m} acquisition) was shorter in pts with co-mutated *FLT3/WT1* without *NPM1* (table 1). Pts who underwent SCT after *WT1* ^{m}acquisition had mOS of 25.7 mos (95% CI 23.8-38.7) compared to 18.3 mos (95% CI 13.2-21.2) (p=0.001) in those who did not undergo SCT. 28% of pts received intensive therapy (+/- VEN) as salvage after acquisition of *WT1* ^{m}without difference in OS compared to those receiving low intensity therapy (66% with VEN). mOS (11.1 vs. 7.8 mos, p=0.12) **.**
In pts ND AML and co-mutant *NPM1/WT1*, *WT1* ^{m} was frequently (75%) subclonal to *NPM1* ^{m} with a mOS NR. However, in pts who initially had *NPM1* ^{m} disease and acquired a *WT1* ^{m} at relapse, *WT1* ^{m} was more clonally co-dominant with *NPM1* ^{m}with a mOS of 15.9 mos (p=0.11). Amongst both cohorts, there was no difference in survival based on sex.

Conclusion

WT1 mutations are enriched in intermediate and adverse risk AML, frequently acquired at relapse, and are associated with overall poor OS in the absence of SCT. Our data suggests that pts with *WT1* ^{m} AML benefit from high intensity induction regimens and SCT at CR1 should be considered in all *WT1* ^{m} pts with ELN2022 intermediate or adverse risk disease. *WT1* mutations should also be considered for inclusion into ELN risk stratification given poor overall survival without SCT.

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Overall Survival by Mutational Status				
	Newly Diagnosed (n=161)		Relapsed/Refractory (n=146)	
	mOS (mos,%)	95% CI (p**)	mOS (mos, %)*	95% CI (p)
Overall Cohort	19.8	16.3 – 30.1	22.8	19.9-24.7
FLT3^{m}/NPM1^{wt}/WT1^{m}	23.3 (32)	18.4-47.9 (p=0.3)	5.9 (21)	4.05-10.2 (p=0.2)
*FLT3^{wt}/**NPM1^{m}/WT1^{m}***	NR (6)	16.4-NA (p=0.05)	15.9 (7)	3.68-NA (p=0.05)
FLT3^{m}/NPM1^{m}/WT1^{m}	13.1 (19)	8.75-NA (p=0.9)	11 (17)	9.28-17.9 (p=0.15)
*FLT3^{wt}/NPM1^{wt}/**WT1^{m}***	18.3 (43)	13.3-30.4	8.03 (50)	5.43-9.47

*Calculated from *WT1* mutation acquisition; includes post-transplant acquisition

**Compared with *WT1^{m}* without *FLT3 or NPM1* co-mutation

Figure 1: Overall Survival in Intermediate Risk ND-AML (SCT vs. No SCT)