soho2023
ELEVENTH ANNUAL MEETING

Outcomes of *WT-1* mutant Acute Myeloid Leukemia: Moffitt Cancer Center Experience

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INTRODUCTION

- Wilms tumor 1 (*WT1*) is a zinc finger transcription factor that is involved with cellular proliferation, apoptosis, and differentiation located on chromosome 11p13. The *WT1* gene has been shown to be highly expressed in several myeloid malignancies, including AML.
- Mutation of the *WT1* gene might play a role in leukemic cell proliferation and impaired cell differentiation. Although initially considered only to be a tumor suppressor gene, *WT1* also has been demonstrated to influence cell survival, proliferation and differentiation and might consequently act as an oncogene.
- The overall incidence of *WT1* mutations is roughly 10-15% of patients with AML. *WT1* mutated AML frequently co-occurs with FMS-like tyrosine kinase 3 (*FLT3)*, and is largely believed to impose poorer outcomes, however the impact of *WT1* mutations remains incompletely understood.

METHOD

- Our study involves 61 AML patients with *WT-1* mutations detected at time of diagnosis. Patients were stratified by age, intensity of initial chemotherapy regimen, ELN classification, allogeneic hematopoietic stem cell transplantation (AHSCT) status, and presence of co-mutations.
- Fifty out of sixty-one pts received intensive chemotherapy (IC) and 11 pts received low intensity (LI)
- LI: (HMA n=4, HMA+Venetoclax n=5, BSC n=2)
- Median OS, co-mutations, CR and HR rates were compared between the two populations

RESULTS

- Median age was 55 years, Median OS (mOS) was 19.1 mo
- ELN: 16% favorable, 39% intermediate and 44% poor risk
- Thirty pts (49%) harbored *FLT-3* ITD
- Thirty pts (49%) relapsed where 14/27 had *FLT-3* ITD and 17/26 had *WT-1* detected at time of relapse
- CR rate was 49% and 11% respectively for IC and LI (p=.05).
- Median OS was 23.6 and 9.6 mo for IC and LI (p.001)
- Among *FLT-3* ITD+ mOS was 23.6 mo and 11 mo respectively for IC versus LI treatment(p=.037)
- mOS was 18.5 and 3.8 mo for IC vs LI w/ *FLT-3*-ITD WT (p.01).
- *FLT-3*-ITD MT/*WT-1* MT group mOS was 36.6 mo with AHSCT compared to 15 mo without (p=.014)
- *FLT-3* wild type/*WT-1* MT the mOS was 30.5 mo with AHSCT compared to 9.8 mo without (p=.016)
- In multivariable analysis adjusting for age, ELN risk group, *FLT-3* , and AHSCT, the HR for overall survival among *WT-1* mutant AML who received LI initial treatment compared to IC was 1.73(95% CI .75-4) (p=.2)
- The HR for AHSCT was .35(95%CI .17-.7) (p.004)

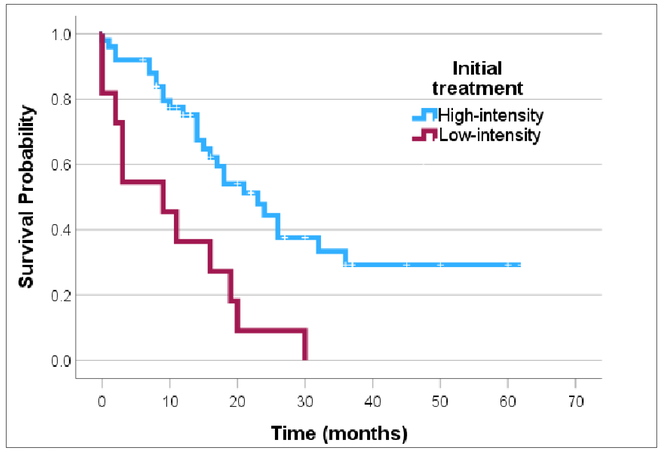


Figure 1a.

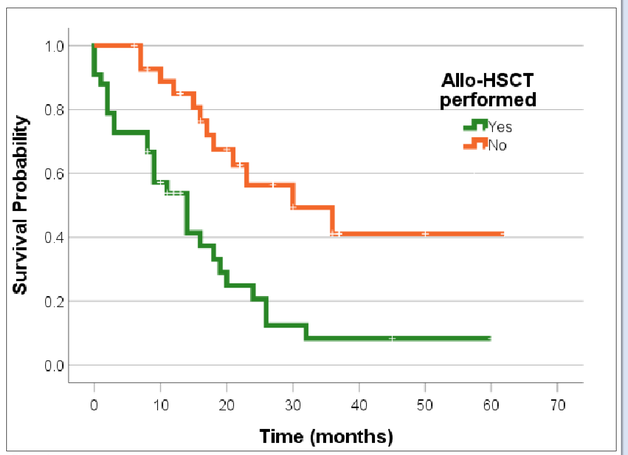


Figure 1b.

Figure 1. Kaplan-Meier survival estimate plots for WT-1 mutated AML patients stratified by (a) intensity of chemotherapy regimen and (b) status of Allogeneic Hematopoietic Stem Cell Transplant (Allo-HSCT)

	IC	LI	p-value
Age (mean)	49	68	<.005
Gender (male)	22 (44%)	5 (46%)	.52
Race (white)	44 (88%)	11 (100%)	.69
ELN • Favorable • Intermediate • Adverse	 10 (20%) 19 (38%) 21 (42%)	 0 5 (45.5%) 6 (54.5%)	.266
Allo-SCT (yes)	27 (52%)	2 (18%)	.042
Allo-SCT in CR1	22 (77.8%)	1 (50%)	.64

CONCLUSIONS

- *WT-1* mutant AML is associated with poor outcomes
- *FLT3*-ITD is the most common co-mutation
- Response rates were better with IC with trend for better OS
- Patients should be considered for AHSCT in CR1 as it provides the only curative option
- Presence of *WT1* mutations should be included in ELN risk stratification due to adverse outcomes

FUTURE CONSIDERATIONS

- Investigating combinations of targeted therapies, chemotherapy agents, and immunotherapies could potentially enhance treatment efficacy
- Deeper insights into the functional genomics of *WT1* mutations could reveal how these mutations impact cellular processes and drive leukemogenesis

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