Distinct Genomic Associations to Predict Acute Myeloid Leukemia (AML) Progression from Myelodysplastic Syndromes (MDS)

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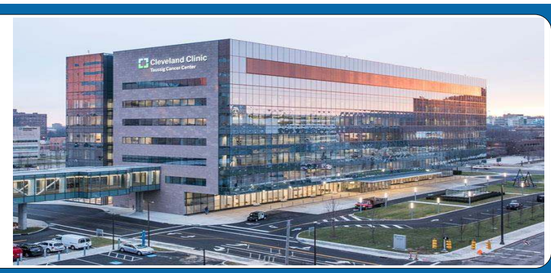


BACKGROUND

- 25% of MDS patients (pts) progress to AML; 15% of those with lower-risk, and ~40-50% of those with higher-risk
- Predicting those who are likely to progress to AML early in their disease course could directly impact treatment decisions

METHODS

Statistical Analyses

- We developed a genomic model that evaluates mutational patterns and their association with AML progression. Development of this model mimics Netflix or Amazon's recommender system in which customers who bought products A and B, are likely to buy C: pts who have a mutation in genes A and B, are then likely to progress to AML
- Association rules using *Apriori* algorithm was used to study the relationship between multiple genes/cytogenetic abnormalities and AML progression in an unbiased approach
- Univariate and multivariate analyses were used to evaluate the impact of mutations on AML progression

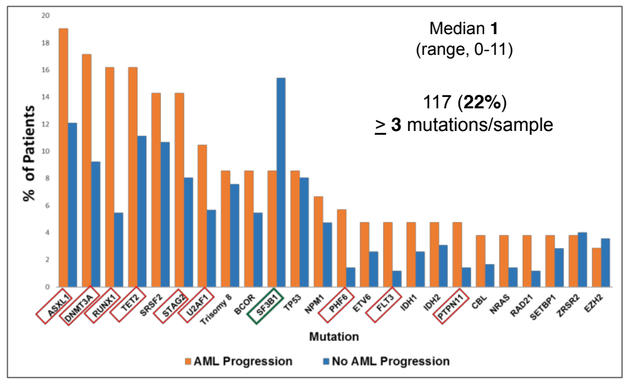
Patient Population

- MDS pts diagnosed between 1/1996 and 9/2016 were analyzed. A panel of 60 gene mutations obtained by next generation targeted sequencing was included.

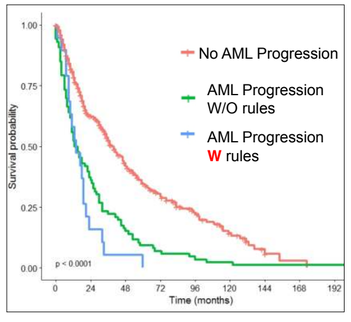
RESULTS

Patient Characteristics	Number / Median (n = 527)	(%) / [range]
Age at diagnosis, years	67	[19-99]
Patients progressing to AML	105	[20]
Time to AML progression (TTP), mo	13	[6.3-29.8]
Gender		
Male	329	(62.0)
Female	198	(38.0)
Clinical Characteristics		
WBC, 10^9/L	3	[0.67 – 37]
ANC, 10^9/L	2	[0 – 24.6]
Hemoglobin, g/dL	10.0	[3.9 – 15.9]
Platelets, 10^9/L	88	[4 – 975]
Median BM Blasts %	2	[0 – 19]
Risk Groups per IPSS		
Low	148	(28.0)
Intermediate –I	235	(45.0)
Intermediate – II	106	(20.0)
High	38	(7.0)
Risk Groups per IPSS-R		
Very Low	78	(14.8)
Low	200	(38.0)
Intermediate	95	(18.0)
High	98	(18.6)
Very high	56	(10.6)
Cytogenetic Risk per IPSS-R		
Very good	15	(2.8)
Good	331	(62.8)
Intermediate	87	(16.5)
Poor	37	(7.0)
Very poor	57	(10.8)

Multivariate Cox Regression Analysis to predict Secondary AML Progression		
Genomic Abnormality	**Hazard Ratio (95% CI)**	**P Value**
RUNX1	2.8 (1.6-5)	*.001*
≥ 3 Abnormalities	1.65 (1.1-2.5)	*.021*
FLT3	**3.1 (1.2 – 8.2)**	***.019***
SF3B1	.417 (.205-.851)	*.016*



Association Rules (sAML)
ASXL1, RUNX1, BCOR
ASXL1, RUNX1, STAG2
ASXL1, STAG2, SRSF2
ASXL1, STAG2, ZRSR2
***ASXL1, TET2,* Trisomy8**
***RUNX1, STAG2,* Trisomy 8**
***TP53, TET2,* Complex Karyotype**



CONCLUSIONS

- MDS pts with ≥ 3 genomic abnormalities, *FLT3* or *RUNX1* have a higher chance of AML progression
- *SF3B1* is associated with lower AML transformation
- Certain gene combinations are associated with higher likelihood of AML transformation
- Machine learning algorithms ("recommender algorithm") may aid in translating genomic data into clinical tools

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