SOHO ANNUAL MEETING 2024

Genomic Evolution of Patients with Myeloid Neoplasms and Known Antecedent Clonal Hematopoiesis

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INTRODUCTION

Clonal hematopoiesis (CH) is the clonal expansion of hematopoietic stem cells (HSCs) with one or more somatic mutations in the absence of a hematologic malignancy.(1)

It is associated with normal aging, but also confers increased risk of cardiovascular comorbidities, and hematologic malignancies, including myeloid neoplasms (MNs) whose outcome remains unknown.

AIM

We aimed to evaluate the clinicopathologic characteristics, and survival outcomes of patients with MN with known antecedent CH.

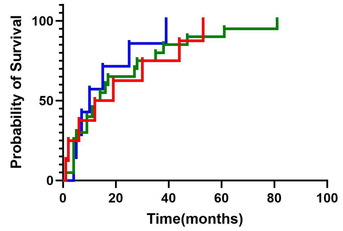
METHOD

- Retrospective review (May 2016-July 2023)
- 32 patients with myelodysplastic syndrome (MDS) , chronic myelomonocytic leukemia (CMML) , and acute myeloid leukemia (AML) with known history of CH.

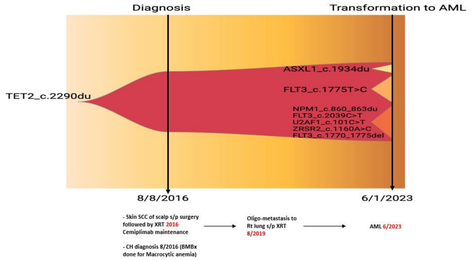
RESULTS

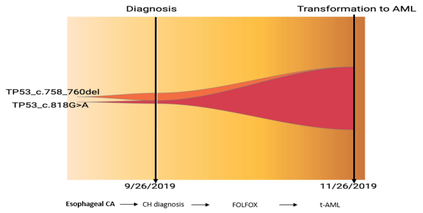
- At time of CH: 75% → cardiovascular comorbidities, 78%→ prior diagnosis of non-myeloid malignancies for which 75% → prior chemotherapy and 25% radiation.
- Clonal Hematopoiesis Risk Score (CHRS): 19% were low, 59% intermediate, and 22% high risk of transformation to MNs.
- The most frequently observed CH-associated mutations were *TET2* (44%), *TP53* (34%)
- Sixty-nine percent had more than one somatic mutation, and 61% had normal cytogenetics.

Time to Transformation to MN by CHRS risk Category



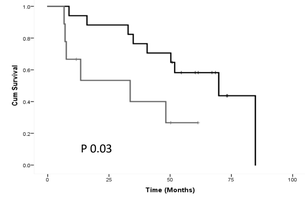
Genomic Evolution from CH to MN





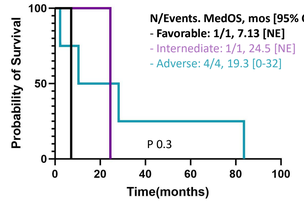
- Median OS, mos [95%CI] from CH: 50.3 [33.7-NE]
- OS from MN:
- MDS: 25[9.2-NE]
- CMML: NR
- AML:1.2 [0.3-NE]

Overall Survival (OS) for MDS & CMML by IPSS-M



MedOS, mos [95% CI]
- Very low- Moderately Low::70 [32-108]
- Moderately High -Very High: 34[1-67]

Overall Survival (OS) for AML by ELN 2017



N/Events. MedOS, mos [95% CI]
- Favorable: 1/1, 7.13 [NE]
- Internediate: 1/1, 24.5 [NE]
- Adverse: 4/4, 19.3 [0-32]

N (%)/Median (range)	Myelodysplastic Syndromes (n=24)	Chronic Myelomonocytic Leukemia (n=2)	Acute Myeloid Leukemia (n=6)	Significant P values
Age	74 (54-86)	55 (36-74)	73 (68-86)	0.032
Males	17 (53)	1 (3)	4 (13)	
Laboratory Values:				
ANC (x10³/L)	2.5 (0.09-12.5)	2.9 (1.7-4.1)	5.2 (0.56-15.3)	
Platelets (x10³/L)	98 (16-217)	146 (119-173)	25 (14-67)	0.002
Hemoglobin (g/dL)	10.3 (7.4-15.7)	10.6 (8.6-12.7)	8.5 (6.8-10.4)	
BM Blasts (%)	3 (1-9)	3 (2-4)	36 (20-72)	0.001
Higher Prognostic Scores:				
IPSS-R (Intermediate-Very High)	9(37)	1(50)	-	
IPSS-M(Moderately High-Very High)	9(37)	0	-	
ELN 2017				
Favorable	-	-	1 (16)	
Intermediate	-	-	1 (16)	
Adverse	-	-	4 (68)	
Treatment:				
Observation	15 (63)	1 (50)	-	0.001
HMA-based therapy	9 (37)	0	2 (34)	0.001
Intensive Chemotherapy	0	0	1(16)	0.001
Hospice	0	0	3 (50)	0.001
SCT	2(8)	1 (50)	0	0.001

CONCLUSIONS

- Risk of progression from CH to MN is amplified with external selective pressures like antineoplastic therapy and radiation.
- These factors are not accounted for in prognostic systems like CHRS.(2)
- Patients often have underlying high-risk clones at the time of CH that expand at the time of MN, though some patients acquire new driver mutations.

FUTURE DIRECTIONS

- Development of new prognostic scores for patients with CH detected at time of treatment for other malignancies, can help predict risk of MN transformation in this patient population.

REFERENCES

1- Khoury et al. *Leukemia* volume 36, pages1703–1719 (2022)
2- Weeks et al. NEJM Evid 2023;2(5)

CONTACT INFORMATION

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