Clonal Hematopoiesis Of Indeterminate Potential Mutations In Neuroendocrine Tumor Patients: Cluster Analysis And Application Of Risk Scores

Harsha Pattnaik[1,2], Guangwei Yuan[2], Teodora Kuzmanovic[3], Akriti G. Jain[3], Zheng Jin Tu[3], David Bosler[3], Hetty E. Carraway[3], Han Yu[2], Renuka Iyer[2], Abhay Singh[3]

Westchester Medical Center, Valhalla, New York, USA
Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA
Cleveland Clinic, Cleveland, Ohio, USA

INTRODUCTION

Clonal Hematopoiesis of Indeterminate Potential (CHIP) mutations are associated with an increased risk of myeloid malignancies and may expand with exposure to radiation or chemotherapy, which are standard therapies for neuroendocrine tumors (NET). We analyzed CHIP mutation prevalence and conducted cluster analysis in NET patients to identify subgroup features that may guide management and targeted interventions.

METHOD

Peripheral blood samples were collected from NET patients. DNA was extracted and processed with a 63-gene myeloid NGS panel with a 2% variant allele frequencies (VAF) cutoff to identify CHIP mutations. Clonal Hematopoiesis Risk Score (CHRS) and Clonal Cytopenia Risk Score (CCRS) were calculated to assess myeloid transformation risk. Tumor grades, demographics and CBC data were collected for cluster analysis.

RESULTS

- In our cohort of 102 NET patients, 24 (23.5%) had CHIP mutations.
- Prevalence of CHIP mutations (6.86%, 7.84%, 8.82%) and CHRS (8.29, 9.31, 9.72; p=0.0298) showed an increasing trend across 10-year age intervals (50-59, 60-69, 70-80 years).
- We identified 2 distinct clusters:
- Cluster 1 (n = 10) had older patients (median age 72 vs. 60 years, p=0.006), higher VAF (0.15 vs. 0.03, p=0.024), elevated CHRS (10.75 vs. 8.00, p <0.001) compared to Cluster 2 (n = 14). Cluster 2 had higher hemoglobin levels (14.45 vs. 12.8, p = 0.002).
- No significant differences were seen in CCRS, tumor grades, WBC and platelet count.
- The clusters remained unchanged after excluding age as a parameter. Agreement between CHRS and CCRS was minimal (0.12, 95% CI -0.29, 0.53; p = 0.57).
- Based on CHRS, 17 patients were identified as low risk with 5-year and 10-year risks of myeloid malignancy at 0.23 ± 0.05% and 0.67 ± 0.08%. Seven were intermediate risk with 5-year and 10-year risks of myeloid malignancy at 2.76 ± 0.48% and 7.83 ± 0.81%. According to CCRS, 19 patients were classified as low risk and 5 as intermediate risk, with 2-year risk of myeloid malignancy of 6.4% and 14.1%.

Cluster analysis of CHIP positive patients

Characteristics	Cluster 1, N = 10[1]	Cluster 2, N = 14[1]	p-value[2]
Age	72 (65, 77)	60 (55, 67)	0.006
Variant allele frequency	0.15 (0.07, 0.27)	0.03 (0.03, 0.06)	0.024
CHRS	10.75 (9.75, 11.00)	8.00 (7.63, 8.88)	<0.001
CCRS	0.00 (0.00, 3.00)	0.00 (0.00, 0.00)	0.12
WBC	5.89 (4.74, 6.26)	6.98 (5.54, 8.42)	0.2
Hb	12.80 (11.80, 13.13)	14.45 (14.13, 15.78)	0.002
Platelet	274 (249, 367)	245 (176, 295)	0.2
Tumor grade			>0.9
Low grade	2 (50%)	6 (67%)	
High grade	2 (50%)	3 (33%)	
Unknown	6	5	

[1]Median (IQR); n (%).
[2]Wilcoxon rank sum test; Fisher's exact test.

CONCLUSIONS

Our study identified distinct clinical and genetic profiles in NET patients prior to chemotherapy or radiation. Once the serial sample analysis is complete, we will assess if existing clusters change or additional clusters emerge after therapy exposure, highlighting potential subgroup-specific implications for patient management.

CONTACT INFORMATION

Harsha Pattnaik

Harsha.Pattnaik@wmchealth.org

ACKNOWLEDGEMENT

NANETS Clinical Investigator Scholarship (NCIS) 2023: A Study of the Evolution of Radio Peptide and Cytotoxic Therapy-related Hematopoietic Molecular Signatures and Role in Predicting Resultant Hematological Toxicity.