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Prevalence of CHIP Mutations in patients with Neuroendocrine Tumors and Role in Predicting Hematologic Toxicity to PRRT and Chemotherapy

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BACKGROUND

In our previous work, we found hematological toxicities from PRRT occur in those with clonal hematopoiesis of indeterminate potential (CHIP) mutations. CHIP mutations carry a formidable risk of progressing to myeloid neoplasia, particularly in cases featuring high-risk mutations. Supported by the NANETS grant, we sought to validate these findings in a larger, independent cohort of neuroendocrine tumors (NETs). We plan future analyses to correlate these findings with treatment options impacting hematopoiesis. Here, we present the molecular signature results prior to chemotherapy and PRRT exposure.

METHODS

Following IRB approval from both institutions, peripheral blood samples from treatment-naïve NET patients were submitted for CHIP mutation analysis. We utilized a 63-gene myeloid NGS panel and used a 2% VAF cutoff to identify CHIP. Extracted DNA was sequenced using anchored Multiplex PCR and Illumina technology, achieving >500X coverage and >98% of targeted regions showing >100X coverage. In future analyses, and with established access to longitudinal samples, we plan to calculate risk stratification scores to predict the risk of hematologic toxicities in these patients.

RESULTS

Here, we present the descriptive statistics of the treatment-naïve NET patients. A total of 102 patients were included in our study. The median age of the cohort was 60.5 years (range: 20-81), with 49 participants (48.04%) being female. Twenty-three (22.5%) patients harbored CHIP mutations (Table). The median age of CHIP+ patients was 65 years vs CHIP negative patients median age was 59 years; p=0.0151. Notably, 9/23 (39%) patients had baseline cytopenias. DNMT3A and TET2 were the most commonly mutated genes. Notably, mutations in high-risk genes [PPM1D (n=3), SF3B1 (n=2), JAK2 (n=1), TP53 (n=1), SF3B1 (n=2); Table] were observed in patients with no prior therapy exposure. Sixteen patients harbored multiple mutations.

Table: Common mutations in NET patients at baseline:

Total Patients with CHIP Mutations (N=23) and Total Unique Mutations (n=32)	
Standard Risk Mutations (N=23)	
DNMT3A	13
TET2	3
Others	7
High Risk Mutations (N=9)	
PPM1D	3
SF3B1	2
MPL	2
TP53	1
JAK2	1

CONCLUSIONS

The high baseline prevalence of high-risk CHIP mutations, which significantly elevate the risk of progressing to overt myeloid neoplasms, along with baseline cytopenia and the presence of multiple mutations in several patients, is concerning. The analysis is currently ongoing, and we will soon include post-treatment data to investigate the correlation between baseline CHIP mutations and the development of hematologic toxicities, bringing us a step closer to developing a risk prediction score for hematologic toxicity.

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