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Prevalence of clonal hematopoiesis (CH) in neuroendocrine tumor (NET) patients prior to lutetium 177 Dotatate (Lu177): A prospective study

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BACKGROUND

Lu177 has shown efficacy in advanced NET with significant hematologic toxicity, including therapy-related myeloid neoplasm (t-MN). CH is defined by acquisition of somatic mutations in hematopoietic stem cells with potential for expansion over time. In this study, we aimed to assess the prevalence of CH in NET patients (pts) prior to Lu177 along with the incidence of cytopenia in NET pts treated with lu177 based on the CH status at baseline

METHODS

Pre-Lu177 blood samples were prospectively collected from 37 NET pts with planned Lu177. Genomic DNA from mononuclear cells was analyzed for CH using a custom panel targeting 229 genes to a targeted depth of >1000X.

RESULTS

A total of 37 NET pts were included (51% male, median age 68); 47% had exposure to either alkylating or platinum agents and most had well-differentiated small bowel NET (51%). Almost half of the pts (n=17; 45.9%) had pathogenic variants meeting the operational definition of CH (*DNMT3A, TET2, PPM1D, TP53, SF3B1, ASXL1*). The most common pathogenic variants were in epigenetic regulators, *DNMT3A* (40%) & *TET2* (13%), and TP 53 (13%). Median follow up was 15.9 months. At baseline, CH pts had a lower platelet count with a median of 180 x 10^9/L (range, 98 - 247) compared to 230 x 10^9/L (range, 125 – 473) without CH (p=0.011). During Lu177 treatment, there was no significant difference in cytopenias between groups, including in grade 3 or 4 cytopenias. Additionally, at 3 months, 6 months, and 12 months follow up, there were no significant differences in hemoglobin, MCV, platelet, leukocytes, neutrophils, or lymphocytes between groups. However, pts with CH were more likely to experience prolonged thrombocytopenia (p=0.025) defined as platelet count <150 for >3 months), but not prolonged anemia (p=0.638) or leukopenia (p=0.756). In total, 3 pts had post- Lu177 CH data available with bone marrow biopsy done. Two of these pts had CH at baseline and one without. Two of these pts were diagnosed with clonal cytopenia of undetermined significance and developed new *PPM1D* mutations. None of the pts developed t-MN.

CONCLUSIONS

CH is observed in a substantial proportion (46%) of NET patients, and our findings suggest that it poses a potential risk for prolonged thrombocytopenia in those receiving Lu177 treatment. Additionally, the clonal expansion of the *PPM1D* mutation following Lu177 treatment may contribute to this risk. Further studies with larger sample sizes are required to comprehensively understand these mutations' impact on hematologic toxicities. Identifying high-risk patients prior to Lu177 treatment enables proactive management to prevent treatment delays.

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