NEUTROPHIL EXTRACELLULAR TRAPS (NETS) IN MYELOPROLIFERATIVE NEOPLASMS (MPNS): IMPACT OF CYTOREDUCTIVE THERAPY

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Background: NETs may contribute to immunothrombosis in myeloproliferative neoplasms (MPNs), a complex process driven by the interaction between the innate immune system and the coagulation cascade. Investigating NETs in MPNs and their potential as biomarkers may provide insights for improving disease management.

Aims: To assess the association between H3.1 nucleosomes, as a surrogate of NETs, and clinical characteristics of MPN patients, and to evaluate the effect of cytoreductive therapy on H3.1 nucleosome levels.

Methods: In this monocentric, prospective study, plasma samples were collected before and after therapy. H3.1 nucleosome levels were measured using the Nu.Q® NETs Immunoassay from 50 µL of K2EDTA plasma.

Results: Forty-two patients were included (50% female): 9 (21%) with essential thrombocythaemia (ET), 18 (43%) with polycythaemia vera (PV), 10 (24%) with primary myelofibrosis (PMF), and 5 (12%) with secondary MF. Baseline samples were obtained from untreated patients (median age 57 years, range 18–77) after a median of 14 months from diagnosis. Overall, 34 (81%) were JAK2V617F, 5 (12%) CALR, 2 (5%) MPL mutated and 1 (2%) was triple negative. JAK2VAF was available in 15 (median 25%, range 7.4–87). Nine (21%) had a prior thrombosis (5 arterial, 4 venous), occurring a median of 45 months before sampling; only 4 were on anticoagulants. Fourteen (33%) had splenomegaly. Baseline H3.1 nucleosome levels varied across MPN subtypes ($p<.001$), being highest in MF compared with ET ($p<.001$) and PV ($p<.001$). No significant difference was observed between driver mutations ($p=0.203$) or thrombosis history. Patients on antiplatelet therapy (n=28) had significantly lower baseline H3.1 levels ($p<.008$). Baseline H3.1 correlated positively with WBC ($r=0.5$, $p=0.001$) and JAK2VAF ($r=0.5$, $p=0.026$). After a median of 12 months on cytoreductive therapy, H3.1 nucleosome levels decreased in 26 patients (62%), with a median 27% reduction ($p=0.058$). Median concentration was 65 ng/mL (range 8.7–937) at baseline vs. 51 ng/mL (3–2770) post-treatment. Despite this trend, H3.1 remained correlated with WBC ($r=0.692$, $p<.001$), JAK2VAF ($r=0.72$, $p=0.003$), neutrophil count ($r=0.60$, $p<.001$), and NLR ($r=0.31$, $p=0.048$). The reduction in H3.1 nucleosomes varied by treatment: 10/15 on ruxolitinib, 6/11 on hydroxycarbamide, 6/10 on pegylated-interferon, and 4/6 on momelotinib showed decreases. Median reductions were 36% with ruxolitinib, 35% with hydroxycarbamide, 27% with momelotinib, and −6% with pegylated-interferon.

Conclusion: H3.1 nucleosome levels varied across MPN subtypes, with higher concentration observed in MF. Prior antiaggregant therapy was associated with lower levels. Cytoreductive therapy reduced H3.1 nucleosome levels in 62% of patients, with the greatest decrease in PV. This is the first study to assess the impact of JAKi, on NETs levels in pre and post-treated MPN patients.