Abstract: P1029

Title: *JAK2*-CHIP IS ASSOCIATED WITH SIMILAR RISK OF CARDIOVASCULAR DISEASE AS *JAK2*-MPN

Abstract Type: Poster Presentation

Session Title: Myeloproliferative neoplasms - Clinical

Background:

Clonal hematopoiesis of indeterminate potential (CHIP) is defined as the presence of an expanded somatic blood cell clone in persons without a known hematologic disorder at a variant allele frequency (VAF) of greater than 2%. CHIP increases the risk for hematologic malignancies and cardiovascular disease (CVD). Mutations in a small subset of genes underlie CHIP, including in the *JAK2* gene which can progress to myeloproliferative neoplasms (MPNs) such as polycythemia vera (PV), essential thrombocytosis (ET) and myelofibrosis (MF). MPNs increase the risk of venous and arterial thromboses, though the extent to which *JAK2*-CHIP may be associated with such events is yet to be fully elucidated. It is also unclear to what degree *JAK2*-CHIP and *JAK2*-mutated MPNs are associated with complications of CVD.

Aims:

We first aimed to determine the rates of venous and arterial thrombosis patients with *JAK2*-CHIP. Secondly, we aimed to characterize to what extent *JAK2*-CHIP is associated with CVD and how this compares to *JAK2*-mutated MPNs.

Methods:

We used exome sequencing data from the MGB Biobank encompassing approximately 54,000 patients to identify 120 with *JAK2* VAF greater than 2%. 51 patients had a diagnosis of MPN by WHO 2016 criteria, 42 patients did not carry a diagnosis of MPN but were assumed to based on blood counts and were excluded from the study. We identified 29 patients with *JAK2*-CHIP who had no other known lifetime hematologic disorders including MPNs and normal cell counts. Two of these patients progressed to an MPN and were excluded from the study. We performed a retrospective analysis of thrombosis and CVD patients with *JAK2*-CHIP and *JAK2*-mutated MPNs.

Results:

Patients with *JAK2*-CHIP and *JAK2*-mutated MPNs had similar demographic distributions by age, gender, BMI, and CVD risk factors. Patients with *JAK2*-mutated MPN had either PV (n= 28, 55%), ET (n= 21, 41%) or MF (n=2, 4%). Median *JAK2* VAF was lower for *JAK2*-CHIP as compared to JAK2-mutated MPNs (median VAF *JAK2*-CHIP=16.2%, median VAF *JAK2*-mutated MPN=28%, p-value=0.018). Median follow-time for patients with *JAK2*-CHIP was 4.5 years and for *JAK2*-mutated MPN was 7.0 years (p-value=0.01). 88% of patients with *JAK2*-mutated MPN were on cytoreductive therapy. Rates of venous thrombosis were comparable across these groups (14.8% vs. 21%, p-value = 0.46). 70% of venous thrombotic events in patients with *JAK2*-mutated MPN occurred within 2 years of MPN diagnosis, and 50% prior to their diagnosis. We found similar rates of arterial thrombosis across these groups, as evidence by ischemic stroke (11% vs. 12%, p-value =0.92) and acute coronary syndrome (7.4% vs. 5.8%, p-value=0.78). Complications of CVD were also comparable with rates of arrhythmias (26% vs. 13%, p-value = 0.17) and heart failure with either systolic or diastolic dysfunction (20% vs. 16%, p-value=0.64). Echocardiogram data was available for 70% of patients and showed similar ejection fractions (60.8% vs 60.7%, p-value=0.98), RVSP (37 vs 34 mmHg, p-value=0.37), and rates of moderate to severe valvular disease (13% vs. 12%, p-value=0.30).

Summary/Conclusion:

We found that *JAK2*-CHIP is associated with elevated risk of thrombosis, consistent with prior studies. Rates of thrombosis and CVD complications were similar between patients with *JAK2*-CHIP and those with *JAK2*-mutated MPN. These results highlight the importance of considering thrombotic and CVD complications in early precursor

stages of hematologic disorders such as CHIP.

Keywords: Clonal hematopoiesis of indeterminate potential