An evaluation of double or triple positivity in JAK2 positive Essential Thrombocythaemia and Primary Myelofibrosis

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Background

- The JAK2 c.1849G>T; p.(Val617Phe) mutation, commonly referred to as JAK2 V617F, is identified in approximately 50% of cases of Essential Thrombocythaemia (ET) and Primary Myelofibrosis (PMF)

- Other somatic mutations commonly identified in ET and PMF include those in the MPL gene which are found in approximately 4-7% of patients, and the CALR gene which are detected in approximately 20-35% of cases

- Different clinical phenotypes have been described when mutations in these genes occur in isolation

- There is little published literature on the prevalence of dual or triple positivity for driver mutations in JAK2, CALR and MPL in these conditions

Aims

- To identify the proportion of patients with JAK2 V617F positive ET or PMF who have additional somatic mutations in the CALR and MPL genes

- To determine whether additional genetic testing is necessary in patients found to have the JAK2 V617F mutation

Methods

- Retrospective analysis of all JAK2 V617F positive cases identified at our centre

- Cases were subdivided into the following disease groups: Polycythaemia Vera (PV), ET or PMF

- ET and PMF cases which were also tested for common CALR and MPL mutations between August 2014 and February 2019 were identified

- The proportion of dual or triple mutations was determined for both ET and PMF

- DNA extracted from blood samples was analysed for the following mutations: JAK2 c.1849G>T; p. (Val617Phe) [V617F]; MPL c.1544G>T; p.(Trp515Leu) [W515L]; insertions or deletions in CALR exon 9 based on GenBank sequences NM_004972.3, NM_005373.2 and NM_004343.3, respectively. JAK2 and MPL mutations were detected using fluorescent allele specific PCR and capillary electrophoresis. CALR insertions and deletions were detected using fluorescence based PCR fragment length analysis.

Results

- A total of 116 cases of JAK2 positive ET were detected

- 97 patients with ET were also tested for CALR and MPL mutations.

  - There were only 2 (2.1%) cases which were JAK2 and CALR positive

  - Dual positivity for JAK2 and MPL accounted for only 3 (3.1%) of cases

  - No cases of ET were triple positive

- 16 patients were diagnosed with JAK2 positive PMF

- 12 were tested for presence of other mutations

  - There were no cases of dual or triple positive PMF

Discussion

- In this cohort there was a very low detection rate for dual positivity for driver mutations in the JAK2, CALR and MPL genes and there were no triple positive cases

- Interestingly, all the cases of dual positivity were in ET patients with none of the PMF cohort having an additional somatic mutation in one of these genes

- Given the very low prevalence of dual/triple positivity and lack of data as to whether there is a clinical impact of having a mutation in more than one of these genes, there is an argument to not test for MPL or CALR in JAK2 positive ET or PMF patients

- The analysis was limited to the most common mutations and did not exclude the presence of less common mutations in JAK2 exon 12 or MPL exon 10; however, the vast majority of JAK2 positive patients have the JAK2 c.1849G>T; p.(Val617Phe) mutation and about 80% of MPL mutations are reported to be MPL c.1544G>T; p.(Trp515Leu).

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