Irish Journal of Medical Science (1971 -) (2019) 188:1459–1460
https://doi.org/10.1007/s11845-019-02018-3

LETTER TO THE EDITOR

No indication for *CALR* mutation analysis in Irish patients presenting with deep vein thrombosis or pulmonary embolism

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Received: 19 March 2019 / Accepted: 3 April 2019 / Published online: 11 April 2019

Dear Sir,

The classical Philadelphia chromosome-negative myeloproliferative neoplasms (MPN) include polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF). These diseases are clinically characterised by a propensity for both thrombosis and bleeding with the mainstay of MPN treatment being to limit these thrombotic episodes and prevent leukaemic transformation with the use of antiplatelet therapy and cytoreduction [1]. The proliferation of myeloid cells in the majority of these MPN is the result of constitutive activation of the intracellular JAK-STAT pathway as a result of acquired driver mutations of the *JAK2*, *CALR* and *MPL* genes. The most common driver mutation is the *JAK2* V617F present in 95% of PV and 50–60% of ET and PMF patients. Insertion/deletion mutations of *CALR* exon 9 are the next most frequent molecular drivers and are present in 60–80% of *JAK2* wild-type ET and PMF. MPN patients harbouring *CALR* mutations have a significantly reduced rate of thrombotic episodes compared with their *JAK2* V617F-mutated counterparts [2]. Additionally, the *JAK2* V617F is detected at a consistent level in patients presenting with thrombosis at uncommon sites such as splanchnic or cerebral vein thrombosis and also at a lower frequency in patients presenting with a deep vein thrombosis (DVT) or pulmonary embolism (PE) [3]. Therefore a requirement exists to determine the clinical value of screening for *CALR* mutations, if *JAK2* V617F negative, in patients presenting with DVT and/or PE in the Irish population.

An audit was therefore performed on all requests for *CALR* mutation analysis received at a centre for haematology malignancy molecular diagnostics. A total of 2424 requests were received between January 2014 and December 2018 inclusive. Of these, 136 (5.6%) had the clinical details provided of unprovoked DVT and/or PE and were all found to be *JAK2* V617F-negative. The median age was 40 years (range 17 to 81 years) and comprised 74 males and 62 females. The method for detection of *CALR* mutations remained unchanged throughout the audit period. A *CALR* mutation was not detected in any of these 136 patients.

This succinct but instructive audit is in concordance with previous studies that have found no value in screening for *CALR* mutations in those patients with either a first or recurrent venous thromboembolism [4, 5]. Of note is the relatively low median age of the population in whom requests were received, possibly reflecting a broader search for the underlying molecular cause of an unexplained thrombosis in younger patients. The diagnosis of MPN requires consideration of clinical, haematological, histopathological, and molecular criteria and therefore, in patients presenting with a DVT and/or PE without any other MPN features, the above evidence implies that *CALR* mutation analysis is not warranted in the thrombophilia work-up of such patients.

Compliance with ethical standards

This study was performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from participants at the referring centres.

Conflict of interest The author declares that he has no conflicts of interest.

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