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LETTER TO EDITOR

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ANAGRELIDE AND THE *CALR* MUTATION ALLELE BURDEN IN ESSENTIAL THROMBOCYTHEMIA

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The myeloproliferative neoplasm of essential thrombocythemia is characterized by a sustained peripheral blood thrombocytosis, increased numbers of morphologically abnormal megakaryocytes in the bone marrow and clinically by episodes of thrombosis or hemorrhage and the propensity to transform into myelofibrosis or acute myeloid leukemia. The main treatment goals are therefore to prevent thrombotic events and to inhibit transformation with antiplatelet and myelosuppressive drugs, respectively. The pathogenesis of essential thrombocythemia is largely defined by three types of driver mutation, namely the *JAK2* V617F, *CALR* exon 9 and *MPL* exon 10 mutations. Significant improvements have been in the treatment of the related myeloproliferative neoplasm of primary myelofibrosis with JAK1/2 inhibitors, but agents such as interferon and anagrelide remain relevant therapeutic options in the modern treatment algorithm for essential thrombocythemia [1]. While hydroxyurea appears to have no effect in inducing molecular responses, reductions in the *CALR* mutation allele burden have been described in some essential thrombocythemia patients treated with interferon alpha and the JAK1/2 inhibitor ruxolitinib [2, 3]. Any effect of anagrelide on the mutant *CALR* allele burden in any essential thrombocythemia patients has not been previously described.

A 75-year old male presented with an isolated thrombocytosis of 703 • 10^9/l. Bone marrow morphology was consistent with a diagnosis of essential thrombocythemia with clustering of increased, hyperlobulated megakaryocytes and focal reticulin deposition. The *JAK2* V617F was not detected. The patient commenced aspirin (75 mg) immediately and was monitored. Due to an increasing platelet count (801 • 10^9/l) and white cell count (20.2 • 10^9/l), hydroxyurea (500 mg) was started 25 months post diagnosis. In the absence of a hematological response (platelet count 642 • 10^9/l), anagrelide (0.5 mg once daily) was added increasing to 1.0 mg and 1.5 mg once daily over the following eight months with the patient achieving a hematological remission (platelet count 251 • 10^9/l and white cell count 4.2 • 10^9/l). At 55 months post-diagnosis, *CALR* mutation analysis was performed on peripheral blood genomic DNA as previously described [4] and detected a 52 base pair deletion (type 1 mutation) in *CALR* exon 9 with an allele burden of 54.2%. Retrospective evaluation of the archival peripheral blood DNA from diagnosis revealed the same mutation present at an allele burden of 36.7%. The platelet count (321 • 10^9/l) and white cell count (7.0 • 10^9/l) remain within normal range.

Despite anagrelide therapy, no impact on the *CALR* mutation allele burden was evident in this instance. While some emerging evidence suggests that driver mutation status may impact on the clinical response [5, 6], the above observation is broadly in line with the finding that in essential thrombocythemia, anagrelide therapy also does not impact on the *JAK2* V617F allele burden [7, 8]. While interferon and JAK1/2 inhibitors are known to exert some of their effects through disruption of immune responses, the full mechanism of action of anagrelide remains unclear with the primary effect being inhibition of megakaryocyte maturation and proplatelet formation [9]. This inability to directly target the malignant clone may reflect the inability of anagrelide to induce molecular responses in essential thrombocythemia, if indeed deep responses are required for long-term survival. This observation requires confirmation in independent patient cohorts.

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CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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