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Letter to the Editor

FIP1L1/PDGFRA is a molecular marker of chronic eosinophilic leukaemia but not for systemic mastocytosis

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Sir,

During the past decade, a number of molecular markers specific for haematological malignancies have been identified. For chronic eosinophilic leukaemia (CEL) [1], one recurrent molecular marker is the FIP1L1/PDGFRA fusion gene product that exhibits tyrosine kinase activity and represents a target of imatinib unless the gene is specifically mutated [2,3]. Over the past few years, an attendant discussion about the relationship of FIP1L1/PDGFRA to systemic mastocytosis (SM) has ensued [3]. In this letter, we wish to provide the following comments to clarify this issue.

In SM, the frequency of associated haematological non-mast cell disorders (AHNMD) is relatively high [4–6]. Using KIT D816V as a marker of SM, it has been noted that the AHNMD usually arises from the same clone [7,8]. Even if KIT D816V is not detected in the AHNMD, both malignancies may be of monoclonal origin. Because of therapeutic implications, the consensus has been to incorporate a specific category of SM in the World Health Organization (WHO) classification of mastocytosis, termed SM-AHNMD [9,10].

Now, a number of reports have commented that patients with CEL often present with an increase in bone marrow mast cells [2,3]. These mast cells usually are spindle-shaped and display aberrant expression of CD25 [3], features that otherwise are found only with mast cells in SM [9]. In most CEL patients, however, criteria for SM [9,10] are not fulfilled. This is because the mast cells are diffusely distributed, do not form aggregates and do not display KIT D816V. Nevertheless, in some CEL patients, mast cells do form multifocal clusters consistent with the diagnosis SM [3]. These patients are appropriately classified as SM-CEL. However, in these patients, the molecular defect, FIP1L1/PDGFRA, is not indicative of SM, but is indicative of the AHNMD, i.e. CEL. It is noteworthy that in these patients, disease symptoms are due to increased eosinophils, and do not overlap with symptoms of SM. Imatinib therefore is prescribed in these patients to bring the eosinophil number under control, but not to treat the SM-component of the disease, which is indolent. Interestingly, most patients with SM-CEL do not have a detectable KIT mutation, which is of importance as KIT D816V confers resistance against imatinib. Thus, in most patients with typical (KIT D816V-positive) SM, therapy with imatinib is not recommended.

Regardless of the presence or absence of FIP1L1/PDGFRA, patients with SM may present with eosinophilia [4,6,9,10]. Thus, in SM, eosinophilia must be considered as a 'pre-diagnostic' checkpoint (SM-eo) at which molecular markers need to be determined, but is not a final diagnosis or decision point at which treatment with imatinib or other drugs can be recommended. Rather, only a complete staging and grading of symptoms and findings [9,10] and a consecutive search for targets will yield the information necessary for treatment decisions and drug-selection [3,9,11]. This is important as patients with indolent SM usually have a normal life expectancy and do not require cytoreductive or targeted drugs, even when presenting with eosinophilia.

Therefore, in order to establish the correct diagnosis and select the appropriate approach to management, we recommend the use of WHO criteria [9,10] in all patients with SM, including those with eosinophilia (SM-eo).

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