Hematology & Medical Oncology

Commentary ISSN: 2398-8495

# Neutrophilic progression in the myeloproliferative neoplasms: molecular insights and potential therapeutic implications

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Disease evolution of the classical Philadelphia chromosome-negative myeloproliferative neoplasms (MPN) usually manifests as either myelofibrotic transformation of polycythemia vera (PV) and essential thrombocythemia (ET) or to a blast crisis resembling acute myeloid leukemia (AML) that can occur in PV, ET or primary myelofibrosis (PMF) [1,2]. An alternative but less well documented course is that of neutrophilic progression. Throughout the literature there exist sporadic case reports of PV, or more rarely PMF, progressing to or terminating in a marked hyperleukocytosis often resembling chronic neutrophilic leukemia (CNL) and which have exhibited a poor overall survival [3-10]. Since the discovery of activating *CSF3R* mutations of exons 14 and 17 in patients with CNL [11], it has become clear that these mutations are now considered a hallmark of CNL with identification rapidly incorporated into classification guidelines [12,13]. The most common CNL-associated *CSF3R* mutation is the T618I that activates the JAK-STAT pathway, providing a rationale for targeted therapy with JAK1/2 inhibitors [11], borne out by some clinical evidence of efficacy [14-16]. Given that a diagnosis of CNL is now nearly defined by the presence of *CSF3R* mutations, the aforementioned proposed CNL transformation of MPN (and treatment with JAK1/2 inhibitors) can be largely dispelled by proving their absence.

Two recent case studies have illuminated the molecular basis of this rare neutrophilic progression. A patient with longstanding *JAK2* V617F-positive PV developed a *BCR-ABL1*-negative hyperleukocytosis without bone marrow dysplasia, fibrosis, or an increase in myeloblasts, mimicking CNL but with a persistence of morphological features of the underlying PV. Sanger sequencing of *CSF3R* exons 14-17 did not detect any mutations [17]. A next-generation sequencing targeted for myeloid malignancies was applied to sequential samples from a *JAK2* V617F-positve PMF patient undergoing such a neutrophilic progression. This approach again did not again detect any mutations in *CSF3R* exons 14 and 17 but demonstrated acquisition of a single *NRAS* mutation coinciding with the hyperleukocytosis, independent of a stable *JAK2* V617F allele burden [18]. The RAS/RAF/MEK pathway interacts with JAK/STAT signalling and is necessary for G-CSF directed proliferation in normal hematopoiesis. Regulation of MEK activity is central to the equilibrium between proliferation and differentiation responses to G-CSF and therefore constitutes a therapeutic target in this case of neutrophilic progression. Clinically available inhibitors of MEK, such as trametinib, have exhibited some effectiveness in *NRAS* mutated myeloid malignancies [19] and in a rare case of hyperleukocytosis in a patient with *NRAS* mutated atypical chronic myeloid leukemia [20].

The possibility therefore exists that those historical CNL *JAK2* V617F-positive cases might represent patients with polycythaemia vera or primary myelofibrosis presenting in this terminating neutrophilic stage [21-23]. Incidental evidence supporting this speculation comes from the favorable clinical response of sporadic *JAK2* V617F-positive CNL patients treated with interferon and hydroxyurea: agents with proven efficacy in the classical MPN [24-26].

Evaluation of the molecular landscape by next-generation sequencing approaches in such uncommon MPN evolution events therefore has the capacity to reveal the underlying molecular landscape and potentially provide targets for specific inhibitors. However, it must also be appreciated that epigenetic and germ line factors also play a role in MPN development and progression. Further understanding of this rare neutrophilic progression of MPN will come from recognition and investigation of additional cases.

## Authorship and contributorship

The author is the sole contributor to the article.

## Acknowledgements

None

## Funding

None

## Competing interests

The author declares no competing interests

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***Key words:*** *mutations, myeloproliferative neoplasms, neutrophilic progression, targeted therapy*

**Received:** December 03, 2017; **Accepted:** December 22, 2017; **Published:** December 26, 2017

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