HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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Scientific Comment

# Inflammatory picture of Philadelphia-negative myeloproliferative neoplasms☆

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In this issue of the Hematology, Transfusion and Cell Therapy Journal, Cacemiro et al. evaluated the plasma cytokine profile of 47 patients with Ph-negative myeloproliferative neoplasms (MPN) [essential thrombocythemia (ET), primary myelofibrosis (PMF), and polycythemia vera (PV)] and of healthy subjects.[1] They demonstrated increased levels of pro-inflammatory cytokines in MPN patients and higher levels of interferon (IFN)-γ-induced protein 10 (IP-10) in PMF patients with the *JAK2 V617F* mutation. They found differences in the cytokine profile among the three MPN disorders, including increased levels of IL-12p70, IL-17A, and RANTES in PMF, showing that MPN, in particular PMF, have altered inflammatory profiles. However, their sample population did not make clinical and prognostic implications of their findings possible.

What is the clinical relevance of the altered cytokine levels in MPN? Are they related to constitutional symptoms, transformation or evolution to fibrosis? Do they have an impact on the risk of thrombosis or response to JAK-2 inhibitors?

In a cohort of patients with ET and PV, Pourcelot et al. showed increased plasma levels of inflammatory cytokines (IL-1, IL-2, IL-6, IL-8, IL-12, TNFα and IFN-γ). The levels of the growth factors, granulocyte-macrophage colony-stimulating factor (GM-CSF), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) were also elevated. They observed that a subgroup of PV patients with vascular complications had significantly different concentrations of IL-12 (p70) and GM-CSF compared to patients with no vascular complications.[2] A study by Tefferi et al. evaluated the cytokine plasma levels of 127 patients with PMF, and observed significantly higher levels of several cytokines and decreased levels of IFN-γ. Increased levels of IL-8, IL-2R, IL-12 and IL-15 were predictive of inferior survival in the multivariate analysis. IL-8 levels predicted leukemia-free survival, which was also associated with ≥1% circulating blasts. These authors also found an association of IL-8 levels with constitutional symptoms and IL-2R and IL-12 levels with transfusion needs. Stratification of patients identified lower survival rates in patients with increased IL-8/IL2R levels. Patients with intermediate-1 and intermediate-2 risk according to the Dynamic International Prognostic Scoring System plus model also showed that cytokine levels influence survival.[3]

Other authors showed that targeting MF-associated cytokines with JAK-2 inhibitors such as ruxolitinib caused reductions in plasma levels of C-reactive protein, IL-1Rra, MIP-1β, TNF-α and IL-6, and was associated with improvements of constitutional symptoms and splenomegaly.[4]

Regarding the evolution of fibrosis, increased levels of IL-8, oncostatin-M, lipocalin-2, transforming growth factor (TGF)-β1, PDGF, FGF, VEGF and inhibitors of matrix metalloproteinases have been associated with the development of fibrosis.[5,6] Megakaryocytes produce PDGF and VEGF, which lead to bone marrow fibrosis and collagen production.[7]

Finally, two inflammatory biomarkers, which are markers of thrombosis and atherogenesis in the general population,

DOI of original article: http://dx.doi.org/10.1016/j.htct.2017.12.003.

☆ See paper by Maira da Costa Cacemiro et al. on pages [120–131].

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https://doi.org/10.1016/j.htct.2018.01.005

were recently identified as prognostic markers in MPN. Barbui et al. evaluated 244 patients with ET and PV and found that the thrombosis rate was higher in the tertile with the highest C-reactive protein levels and lower in patients with the highest pentraxin-3 levels.[8] Lussana et al. demonstrated a strong correlation between the JAK2 V617F allele burden and PTX3 levels.[9]

In summary, Cacemiro et al. showed that increased cytokine levels are associated with MPN physiopathology.[1] These markers may be useful for risk stratification of Ph-negative MPN and help in the clinical management and by combining treatments that target clonal hematopoiesis and inflammation.

## Conflicts of interest

The author declares no conflicts of interest

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