Perspectives on chronic inflammation
in essential thrombocytemia, polycythemia vera
and myelofibrosis

Is chronic inflammation a trigger and driver of clonal evolution and
development of accelerated atherosclerosis and second cancer?

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Abstract

The morbidity and mortality of patients with the chronic Philadelphia-negative chronic myeloproliferative neoplasms (MPNs), essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF) are mainly caused by cardiovascular diseases, thrombohemorrhagic complications and bone marrow failure due to myelofibrosis and leukemic transformation. In the general population chronic inflammation is considered of major importance for the development of atherosclerosis and cancer. MPNs are characterized by a state of chronic inflammation, which is proposed to be the common denominator for the development of “premature atherosclerosis”, clonal evolution and second cancer in patients with MPNs. Chronic inflammation may both initiate clonal evolution and catalyze its expansion from early disease stage to the myelofibrotic burnt-out phase. Furthermore, chronic inflammation may also add to the severity of cardiovascular disease burden by accelerating the development of atherosclerosis which is well described and recognized in other chronic inflammatory diseases. A link between chronic inflammation, atherosclerosis and second cancer in MPNs favours early intervention at the time of diagnosis (statins and interferon-alpha2), the aims being to dampen chronic inflammation and clonal evolution and thereby also diminish concurrent disease-mediated chronic inflammation and its consequences – accelerated atherosclerosis and second cancer.
**Introduction**

The Philadelphia-negative chronic myeloproliferative neoplasms (MPNs) - essential thrombocythemia (ET), polycythemia vera (PV, and primary myelofibrosis (PMF) - are clonal hematopoietic stem cell disorders, in which the JAK2 V617F mutation is detected in >95% of PV patients and in about 50% of patients with ET and PMF. Transitions between disease entities are common, which may depict a biological continuum from early disease to the advanced myelofibrosis stage. Since the discovery of the JAK2V617F mutation other mutations have been described, contributing to unregulated JAK-STAT (Janus kinase/signal transducer and activator of transcription) signaling, modulation of transcription and accumulation of oncoproteins. However, it is not established how all these abnormalities interact and influence disease initiation, clonal evolution and terminal blast crisis. Several of these mutations are considered to be secondary events whereas the initiating hit(s) and the driver of clonal evolution in these neoplasms are unknown. Elevated biomarkers of chronic inflammation and chronic inflammatory and autoimmune diseases have been described in all disease entries being most common in the advanced myelofibrosis stage.

Based upon evidence obtained from clinical observations, experimental and molecular studies it is argued that chronic inflammation may be both an initiator and a driver of clonal evolution in patients with MPNs. The perspectives of chronic inflammation as the underlying mechanism is discussed with particular focus upon the early development of accelerating atherothrombotic disease (premature atherosclerosis), thrombosis, and second cancer. It is concluded that this novel interpretation of current data – in perspective – supports the contention of early therapeutic intervention with agents having the potential to dampen chronic inflammation and impair clonal evolution. Statins and interferon-alpha2 (IFN-alpha2) may be highly important in this setting, IFN-alpha2 being able to induce sustained molecular remissions in a subset of patients and accordingly may reduce the risk of thrombohemorrhagic complications, myelofibrotic or leukemic transformation and the development of second cancer.

**Does chronic inflammation contribute to cardiovascular morbidity and accelerated atherosclerosis in patients with essential thrombocythemia, polycythemia vera and primary myelofibrosis?**

Chronic inflammation has an important role in the development of atherosclerosis and for years it has been evident that chronic inflammatory diseases – eg. rheumatoid arthritis (RA),
psoriasis \textsuperscript{10} and systemic lupus erythematosus (LED) \textsuperscript{11} - are associated with accelerated atherosclerosis (premature atherosclerosis). In addition, chronic inflammation has an important impact upon the development of premature atherosclerosis in patients with diabetes mellitus (DM) as well.\textsuperscript{12,13} Furthermore, chronic inflammation also indirectly predisposes to venous thrombosis, since an association between atherosclerosis and venous thrombosis has been documented.\textsuperscript{14}

C-reactive protein (CRP) is a sensitive marker of inflammation.\textsuperscript{15} Since CRP influences endothelial function, coagulation and fibrinolysis, oxidation of LDL and plaque stability and CRP is present in atherosclerotic plaques it is currently debated whether CRP has a causal role in the development of cardiovascular disease, being a mediator of vascular disease.\textsuperscript{17} In regard to CRP as a vascular risk factor a most recent metaanalysis study concluded that the CRP concentration has continuous associations with the risk of coronary heart disease, ischemic stroke and vascular mortality.\textsuperscript{18} Chronic inflammation also triggers in vivo activation of platelets, leukocytes and endothelial cells\textsuperscript{19-21} which all are of major importance during thrombus formation. The inflammatory process in the vessel wall may be reflected in peripheral blood by elevated blood levels of several inflammatory cytokines and other acute-phase reactants, including CRP and interleukin-6, which both are raised in unstable angina and myocardial infarction, high levels predicting dismal prognosis.\textsuperscript{22} Other inflammatory markers are also elevated, including fibrinogen, interleukin-7, interleukin-8, soluble CD40 ligand, and the C-reactive protein–related protein pentraxin 3.\textsuperscript{23} Activated T cells are deeply involved in the inflammatory process in atherosclerosis and several subsets of inflammatory T cells are increased in the blood of patients with acute coronary syndromes.\textsuperscript{7}

The link between chronic inflammation and atherosclerosis in the general population and between chronic inflammatory diseases and premature atherosclerosis may be translated to patients with MPNs, in whom chronic inflammation may contribute significantly to cardiovascular disease burden and thrombotic complications as well. The pathogenesis of thrombosis in these patients is multifactorial.\textsuperscript{24,25} Thus, in PV-patients the increased hematocrit is considered of importance, although the significance of the hematocrit in the range of 40-55 \% for cardiovascular morbidity has most recently been questioned.\textsuperscript{26} Other contributing factors to abnormal rheology in these patients are leukocytosis, thrombocytosis, circulating leukocyte-platelet aggregates and in vivo leukocyte, platelet and endothelial cell activation.\textsuperscript{27} Importantly,
both leukocytosis and the JAK2V617F mutation have been found to be risk factors for thrombosis.28,29

Most recently, two inflammatory biomarkers - short pentraxin C-reactive protein (CRP) and long pentraxin-3 (PTX3) - have been significantly associated with the number of major thrombotic events in patients with ET and PV.3 Thus, the highest levels of high sensitivity (hs) CRP doubled the risk of thrombosis3 being in accordance with results of several prospective studies.30 The highest levels of PTX3 were associated with a lower thrombosis rate3 implying PTX3 to exert a protective effect against thrombosis. Indeed, deficiency of PTX3 has been shown to promote vascular inflammation and atherosclerosis and elevated levels of PTX3 to be associated with a reduced risk of cardiovascular disease and thrombosis.31

In patients with ET and PV the elevated CRP levels have been explained consequent to clonal myeloproliferation with in vivo cell activation (leukocytes and platelets), giving rise to release of proinflammatory cytokines and other proinflammatory products from leukocytes and platelets.25 In the study by Barbui et al levels of hsCRP also correlated significantly with the JAK2V617F allele burden.3 Accordingly, chronic inflammation might be considered a secondary event elicited by clonal cells. However, in the context of MPNs, elevated leukocyte and platelet counts may not only reflect clonal myeloproliferation but also the impact of chronic inflammation per se upon the clonal cells being featured by an inherent hypersensitivity to growth factor and cytokine stimulation - one of the hallmarks of these neoplasms. In this perspective, chronic inflammation in MPNs may also have a key role in promoting premature atherosclerosis and all its debilitating cardiovascular and thromboembolic complications, the common denominators for their development being elevated leukocyte and platelet counts, elevated CRP levels, and in vivo leukocyte-platelet and endothelial cell activation with a thrombogenic endothelium - abnormalities which altogether are associated with an increased risk of thrombosis and premature atherosclerosis in other chronic inflammatory diseases.6-11,13,19-21

Does chronic inflammation predispose to insulin resistance and diabetes mellitus in patients with essential thrombocytopenia, polycythemia vera and primary myelofibrosis?

Chronic inflammation has been shown to be the link between insulin resistance, obesity and diabetes.12 Indeed, activation of the inflammation cascade, endothelial dysfunction, and procoagulant imbalance are very important pathophysiological mechanisms leading to beta-cell damage, insulin resistance and the vascular complications of diabetes.13
Circulating biomarkers such as TNFalpha, IL-6, C-reactive protein (CRP) (inflammation), vascular cellular adhesion molecule-1, interstitial cellular adhesion molecule-1, E-selectin, von Willebrand factor (endothelial dysfunction), plasminogen activator inhibitor-1, fibrinogen, P-selectin (procoagulant state), and adiponectin (antiinflammation) may all be associated with development of both type 1 and type 2 diabetes. In fact, some studies, particularly in type 2 diabetes, have demonstrated certain biomarkers to have independent predictive value. These biomarkers may also be associated with development of diabetic nephropathy and retinopathy, and, particularly in type 2 diabetes, with cardiovascular events as well. In addition, insulin resistance has been shown to play an important role in the increased frequency of atherosclerosis in patients with rheumatoid arthritis and to be an independent risk factor for atherosclerosis in this disease. Based upon the close association between chronic inflammation and insulin resistance and chronic inflammation as a potentially very important pathogenetic factor contributing significantly to cardiovascular disease burden a disturbed glucose homeostasis might be expected to be present in MPN patients as well – an association which deserves to be explored systematically in a prospective study.

**Does chronic inflammation contribute to hyperuricemia in essential thrombocythemia, polycythemia vera and primary myelofibrosis?**

In the general population hyperuricemia is associated with chronic inflammation, cardiovascular and renal disease. Accordingly, it might be anticipated that hyperuricemia also influences the cardiovascular disease burden in patients with MPNs. However, serum uric acid has not been considered a risk factor for cardiovascular disease in these patients but may indeed be important – elicited by chronic inflammation and the increased cell turn over. The elevated serum uric acid per se may constitute a risk factor for endothelial dysfunction even mild hyperuricemia being a significant independent risk factor for endothelial dysfunction in subjects without the metabolic syndrome. Of note, treatment with allopurinol in patients with chronic kidney disease has been shown to decrease CRP, slow down the progression of renal disease and reduce cardiovascular and hospitalization risk.

**Does chronic inflammation contribute to chronic kidney disease (“MPN-nephropathy”)?**

Most recently, a series of patients with MPNs and chronic renal failure has been described and previous reports reviewed. The designation “myeloproliferative glomerulopathy” was proposed
for this particular entity which may be more prevalent than previously recognized. In regard to the pathogenesis of myeloproliferative glomerulopathy it was proposed that PDGF and TGF-b might likely have an important role when considering that both cytokines are elevated in patients and PDGF is a very potent stimulus of mesangial cell proliferation and induces extracellular matrix production by mesangial cells. The impact of chronic inflammation per se on the development of CKD also has to be considered in these patients. Thus, beyond the known factors predisposing to chronic kidney disease (e.g., obesity, hypertension and diabetes mellitus) there is evidence of a pathophysiological role for inflammation as well. Indeed, chronic inflammation in MPNs may contribute significantly to the progression of CKD by inducing an increase in several inflammatory biomarkers, including CRP and IL-6, which are considered of importance in CKD pathogenesis. Chronic inflammation in CKD also further causes mortality from cardiovascular disease by contributing to the development of vascular calcifications and endothelial dysfunction. The more frequent occurrence of CKD in patients with myelofibrosis as compared to earlier disease stages (ET and PV) may reflect the long-term deleterious influence of chronic inflammation in this patient group. Accordingly, chronic inflammation per se may facilitate renal dysfunction in MPN-patients. The potential of statin treatment to lower disease burden associated with this particular complication deserves to be explored, since statin administration is accompanied by risk reduction in all major vascular events in patients with CKD.

Does chronic inflammation trigger clonal evolution, autoimmunity and second cancer in essential thrombocytemia, polycythemia vera and primary myelofibrosis?

Chronic inflammation is considered of major importance in the development of several cancers, including certain hematological neoplasms. Recently, several molecular and cellular signaling circuits have been identified linking inflammation and cancer - a concept which was already described by Virchow in the nineteenth century when he suggested that chronic inflammation might give rise to malignancy. However, not until more recently the link between inflammation and cancer has been acknowledged, being partly attributed to epidemiological studies, which have generated data indicating chronic infections and inflammation as major risk factors for various types of cancer.

Despite chronic inflammation being well described as having a major pathogenetic role in the development and progression of certain malignant lymphomas, chronic inflammation as a
potential initiating event and a driver of clonal evolution in myeloid cancer has not been focused upon. However, an increased risk of myeloid malignancies in autoimmune conditions has been documented and - most recently - a large Swedish epidemiological study concluded that chronic immune stimulation might act as a trigger for development of the myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). It is intriguing to consider, if previous and concurrent inflammation may also contribute in the pathogenesis and development of ET, PV and PMF. Herein, it is hypothesized that chronic inflammation with ensuing sustained immune stimulation may trigger clonal evolution and also may catalyze and drive the clone from the early disease stage towards the advanced myelofibrosis stage. Accordingly, myelofibrosis may be featured by clinical, biochemical and molecular evidence of an aberrant and dysfunctional immune system, implying a potential risk of autoimmune/autoinflammatory diseases and – in addition – an increased risk of second cancer. Several observations are supportive for this hypothesis. First, as mentioned above, several studies have shown that inflammatory diseases may precede or develop during the course of ET, PV and myelofibrosis. In the Swedish study a prior history of any autoimmune disease was associated with a significantly increased risk of myeloproliferative neoplasm. The “inflammatory” diseases included among others Crohn’s disease, polymyalgia rheumatica and giant cell arteritis and the “autoimmune” diseases included immune thrombocytopenic purpura and aplastic anemia. An association between autoimmunity and myeloid cancer has been known for several years in patients with MDS and various autoimmune phenomena have also been reported in MPN-patients, including immune activity in the bone marrow, circulating immune complexes, complement activation, and autoimmune cytopenias. Second, most recent studies have shown that patients with MPNs have an increased risk of second cancer – both hematological and non-hematological. This risk may be inherent and associated with the particular JAK2 46/1 haplotype. Other pathogenetic mechanisms might be related to the JAK2V617F mutation per se, which has been shown to be associated with an increased risk of second cancer. Third, vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-beta) are potently immunosuppressive cytokines, which are elevated in the circulation and markedly expressed in the bone marrow in MPNs. Both cytokines may induce qualitative and quantitative alterations in immune cells, being responsible for intact tumor immune surveillance (eg. dendritic cells, cytotoxic T-cells, regulatory T cells, NK-cells). Fourth, based upon the association between antecedent chronic inflammatory or autoimmune
diseases and MPNs\textsuperscript{5} and the link between chronic inflammation, autoimmunity and development of other myeloid cancers (MDS and AML)\textsuperscript{46,47} it is tempting to speculate, if chronic inflammation may also elicit clonal myeloproliferative cancer rather than merely being a consequence of clonal myeloproliferation. Most recently, the link between chronic inflammation with elevated levels of several cytokines, including TNF-alpha, and clonal evolution has been substantiated by the findings that TNF-alpha is capable of facilitating clonal expansion of JAK2V617 positive cells in myeloproliferative neoplasms.\textsuperscript{64} Accordingly, chronic inflammation may drive clonal expansion from early disease stage to the burnt-out myelofibrosis stage. Fifth, the hypothesis that chronic inflammation may precede and predispose to the development of MPNs is further supported by the findings that chronic inflammatory diseases – eg.Crohn’s disease\textsuperscript{65,66} - and certain myeloid cancers, including MPNs, share an increased frequency of the JAK2 46/1 haplotype of chromosome 9q\textsuperscript{67,72}, which is present in about 45\% of the normal population. The JAK2 46/1 haplotype may be \textit{“a marker of inappropriate myelomonocytic response to cytokine stimulation leading to increased risk of inflammation, myeloid neoplasms and impaired defence against infection”}, which most recently has been excellently described.\textsuperscript{59} Indeed, the observations by Tefferi et al, that the JAK2 46/1 haplotype confers inferior survival in PMF and increases the risk of myelofibrotic transformation in patients with PV\textsuperscript{71} may reflect enhanced chronic inflammation, contributing to clonal evolution consequent to increased genetic instability (JAK2 46/1 predisposes to additional mutations in the JAK2 gene; JAK2 activation and the JAK2V617F mutation per se induces genetic instability\textsuperscript{73}) but also to cytokine-mediated expansion of the malignant clone.\textsuperscript{59,64,73} Importantly, the epidemiological evidence of an association between antecedent chronic infections and inflammatory diseases and the development of other myeloid cancers (MDS and AML)\textsuperscript{46,47} is suggestive of a similar association in myeloproliferative cancer. Lastly, several studies have shown elevation of a number of cytokines involved in inflammation and immunoregulation\textsuperscript{48,49} and most recently gene expression profiling studies have also evidenced a marked deregulation of several inflammation and immune genes in patients with MPNs\textsuperscript{50,51} - all supporting chronic inflammation and immune stimulation/deregulation to be involved in the pathogenesis of these neoplasms.
NF-Kappa-Beta – the common pathway for chronic inflammation, atherosclerosis and cancer?

The causal relationship at the cellular level between chronic inflammation and atherosclerosis and between chronic inflammation and cancer development includes several pathophysiological processes, all being linked by inflammation and a single transcription factor - NF-κB. Among these the NF-κB pathway has a key role in inflammation and innate immunity but also in promoting tumour development. Accordingly, the NF-κB pathway may provide the link between chronic inflammation, atherosclerosis and cancer in patients with MPNs. Furthermore, NF-κB may have a major role in controlling the ability of the malignant clone to resist apoptosis propagated by tumour-surveillance mechanisms. In this context, the impact of TNF-alpha as a tumor promoter and its ability to facilitate clonal expansion of JAK2V617-positive cells may be of crucial importance.

Do monocytes link atherosclerosis and cancer in patients with MPNs?

Monocytes are key cells of the immune system which is indispensable for the development and progression of both atherosclerosis and cancer. Circulating monocytes increase in number as the atherosclerosis worsens and monocyte migration to the vessel wall is a key event in the growth of atherosclerotic lesions. When accumulating in the vessel wall monocytes differentiate into macrophages and lipid-rich foam cells which are of utmost importance in disease complications. Monocytosis is common in patients with myelofibrosis, in whom it is an independent prognostic factor implying inferior survival. It is intriguing to consider if monocytosis in myelofibrosis – in addition to clonal myeloproliferation – may reflect cardiovascular disease burden as well. Finally, several studies in solid tumors have shown that “tumor-associated macrophages” (TAMs) in the tumor microenvironment promote cancer. It remains to be elucidated if the monocytosis in myelofibrosis is associated with an increased density of TAMs within the bone marrow which may further add to the poor prognosis.
Discussion and perspectives

The morbidity and mortality of patients with MPNs are closely associated with cardiovascular disease burden and clonal evolution with myelofibrotic and/or leukemic transformation. Most recently, epidemiological studies have evidenced that these patients are exposed to an increased risk of both hematological and non-hematological cancer as well. In the context of cardiovascular disease burden, the general concept has been that these complications were primarily attributed to abnormal rheology consequent to the raised hematocrit, leuko- and thrombocytosis and in vivo activation of leukocytes, thrombocytes and endothelial cells. Consequently, activated clonal cells release several proinflammatory products which altogether elicit a state of chronic inflammation. However, another supplementary mechanism may imply that chronic inflammation per se elicits and drives clonal evolution towards the burnt-out myelofibrosis phase. This novel concept is supported by the known link between chronic inflammation and cancer being recognized for several years and most recently also substantiated in myeloid cancer by the association between chronic inflammatory/autoimmune diseases and the subsequent development of MDS and AML. Furthermore, several reports have described the concurrence of chronic inflammatory or autoimmune disease and MPNs, in particular in patients with myelofibrosis. Chronic inflammation and cancer share a common pathway – the NF-κB. In cancer, including the MPNs, NF-κB is misregulated and constitutively active. As such NF-κB turns on the expression of many genes whose products mediate inflammatory and immune responses and genes that sustain cell proliferation and inhibit apoptosis, potentially promoting cancer development. Of note, many of these cytokines - eg. IL1, IL-6, IL-8, TNF-alpha - are elevated in patients with MPNs, in particular in myelofibrosis. In the bone marrow the expression of genes for E-selectin, IL-8 and TNF-alpha may result in neutrophil activation and TNF-alpha-facilitated clonal expansion. In the context that NF-κB controls many genes involved in inflammation and chronic inflammation has a major role in the development of atherosclerosis, this pathway is activated in atherosclerosis as well. Importantly, key regulators of NF-κB are associated with elevated mortality, especially from cardiovascular disease. The NF-kB pathway has been shown to be activated and implicated in the abnormal release of TGF-beta in PMF, implying an important role of NF-κB activation in the development of bone marrow fibrosis. As noted previously, TGF-beta is highly immunosuppressive, impairing the functionality of several immune cells (dendritic cells, NK-cells, cytotoxic T-cells) involved in
tumor immune surveillance.\textsuperscript{61,63} Accordingly, by enhancing TGF-beta release in the bone marrow NF-κB activation may not only promote fibrosis but also indirectly promote expansion of the malignant clone by suppressing immune cells.

The JAK2V617F-mutation induces constitutive activation of downstream signaling pathways, including STAT3/STAT5 with ensuing induction of cell proliferation (STAT5) and neutrophil activation (STAT3).\textsuperscript{90} By triggering the NF-κB and JAK pathways, STAT3 also activates the production of enzymes (metalloproteinases), cytokines (IL-6, IL-10, IL-17, IL-23) and growth factors (VEGF, FGF). Accordingly, STAT3 may be a key regulator of cancer-associated inflammation in MPNs eliciting and sustaining angiogenesis and metastatic potential (egress of CD34 + cells from the bone marrow). In the context of tumor inflammation and immunity STAT3 has a dual function, since STAT3 both promotes pro-oncogenic inflammatory pathways, including NF-κB and IL-6, and also opposes STAT1-and NF-κB-mediated T helper 1 anti-tumor immune responses.\textsuperscript{91}

In the general population leukocytosis is a well known risk factor for cardiovascular disease\textsuperscript{92} and most recently leukocytosis has been shown to be an important risk factor for the development of thrombosis in the MPN-population as well.\textsuperscript{28,29} Furthermore, leukocytosis has a detrimental effect upon survival in patients with “ET”, when these patients are validated strictly according to WHO criteria, implying significantly different survival of patients with WHO-defined ET and early/prefibrotic PMF.\textsuperscript{91} In regard to atherosclerosis a heavy burden of cardiovascular morbidity may be seen already at the time of diagnosis, albeit the risk of cardiovascular death is but moderate as compared to the high risk of death from noncardiovascular causes (mainly hematologic transformations) in a large cohort of patients with PV.\textsuperscript{83} It is tempting to speculate, however, if these patients may actually have an increased risk of developing premature atherosclerosis considering the link between chronic inflammation and atherosclerosis.\textsuperscript{6-13,16-18} Since biomarkers of chronic inflammation are elevated in MPN-patients chronic inflammation may not only have an impact upon the risk of thrombosis but also facilitating clonal expansion mediated via high levels of TNF-alpha in the bone marrow.\textsuperscript{64}

Most recently, gene expression profiling studies have unravelled massive deregulation of a number of genes involved in immune regulation and inflammation\textsuperscript{50,51} adding to the concept that chronic inflammation and immune deregulation may be important in the pathogenesis and progression of these neoplasms.\textsuperscript{50,51} Irrespective of the underlying mechanisms for aberrant inflammatory and immune function deregulation of inflammation and immune genes may drive
clonal myeloproliferation and evolution towards the myelofibrotic burnt-out phase of the disease. Ultimatively, the abnormal immune homeostasis may imply a defective tumor immune surveillance, which may contribute to the increased frequency of second cancer as well.\textsuperscript{52,53} The impressive efficacy of JAK1-2 inhibitor and HDAC-inhibitor treatment in reducing huge splenomegaly, alleviating hypermetabolic symptoms and partly also reducing leuko-and platelet counts\textsuperscript{94-96} may primarily reflect the very potent antiinflammatory effects of both agents. In this context, the rapid resolution of large splenomegaly may be consequent to elimination of reactive immune cells in the spleen more than a direct antitumor effect, being supported by no or minor reduction in JAK2V617-allele burden despite a pronounced reduction in inflammatory cytokines, including TNF-alpha and IL-6.\textsuperscript{94} The concept of chronic inflammation as a likely important contributing factor in MPN-pathogenesis may have several implications. In regard to treatment this concept certainly argues for initial treatment in order to eliminate leukocytosis – a risk factor for thrombosis in the general population and undoubtedly also in this patient group likely an important factor for cardiovascular disease. Statins are standard medications used in cardiovascular diseases - not only due to their cholesterol-lowering effects - but also because statins possess several pleiotropic effects, including very potent antiinflammatory properties\textsuperscript{97}, which collectively by dampening inflammation, activation of leukocytes, platelets and endothelial cells may benefit patients with MPNs and accordingly should be considered already at the time of diagnosis.\textsuperscript{97} Furthermore, in the context of chronic inflammation as a potential promoter of cancer development and progression and these patients indeed have an increased risk of second cancer as well\textsuperscript{52,53} it is also for these reasons important to alleviate the chronic inflammatory drive which is perpetuated by the clonal myeloproliferation per se. The potential role of statins in the treatment of patients with MPNs\textsuperscript{97} has most recently been substantiated by the findings that statins decrease primary MPN cell colony formation and cooperate with JAK inhibitors (both JAK1 inhibitor I and JAK1-2 inhibitor (ruxolitinib) with an enhanced reduction of JAK2-V617F-positive cell growth over single agent treatment.\textsuperscript{98} Likewise, combination therapy with IFN-alpha may be a rational approach\textsuperscript{100} with the potential of inhibiting clonal expansion and thereby interrupting the inflammation-driven increase of several cytokines (eg. TNF-alpha, IL-6), which otherwise might facilitate clonal expansion, release of proinflammatory products from the expanding clone.
and accordingly further enhancement of chronic inflammation and rise in inflammatory cytokines. In conclusion, in the perspective that chronic inflammation and impaired tumor immune surveillance may be important factors in the pathogenesis and progression of these neoplasms it seems rational – in addition to statins - to initiate immune enhancing treatment with IFN-alpha at the time of diagnosis when the tumor burden is the least and accordingly the outcome of IFN-alpha likely the very best. By restoring potentially impaired tumor immune surveillance IFN-alpha may prohibit clonal expansion, myelofibrotic and leukemic transformation and the development of second cancer as well. 99,100

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References


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