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# Signs and Symptoms of Myeloproliferative Neoplasms (MPN), Quality of Life, Social Activity, Work Participation and the Impact of Fatigue in Dutch MPN Patients: A One Country Questionnaire Investigation of 497 MPN Patients

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## Abstract

The main primary symptoms in 363 MPN patients subdivided in 123 ET, 190 PV and 50 MF patients were fatigue, night sweats, pruritis and bone pain. MPN diagnosis was based on symptoms in 56% (n = 203), detected by coincidence in 30% (n = 110) and based on complications in 14% (n = 49). The 497 MPN patients were on treatment with low dose aspirin in 70%, phlebotomy in 42% (mainly PV 91%), hydroxyurea in about 30% of ET, PV and MF, and pegylated interferon-alpha2a in 16% of ET and PV patients at time of evaluation. The MPN patients were limited in physical mobility in 10%, 14% and 24%, limited in the ability to exercise in 15%, 29% and 38% and social activity was restricted in 9%, 11% and 11% of ET, PV and MF patients respectively. Non-retired MPN patients experienced self-reported fatigue as the main reason for the inability to work full-time in 31% of ET, 40% of PV and 59% of MF patients. The top 20 complaints at time of diagnosis in 399 out of 497 (81%) MPN patients was fatigue (81%) equally high in ET, PV and MF patients. Apart from fatigue about 40% to 60% of ET and PV patients presented with aspirin responsive microvascular disturbances. Itching (PV 58% vs ET 30%) and fatigue were much more prominent in PV. About one third of MPN (ET, PV and MF) patients suffered from bone pain. MF patients suffered more frequently from constitutional symptoms of prominent fatigue and night sweats related to pronounced splenomegaly. Before the diagnosis was made in 497 MPN patients, the complaints were ascribed to other causes in 173 (35%): to stress, burned out or overstrained in 41 (24%), to depression or hystery in 14 (8%), migraine of unknown origin in 13 (8%) and to rheuma, hypertension or fibromalgia in a few.

## Introduction

The Dutch Patient Foundation on myeloproliferative neoplasms (MPN) aims to supply information towards MPN patients, to look after their interests, to stimulate contact between MPN patients, and to exchange information and relevant knowledge among medical doctors and MPN patients [1-5]. The Dutch MPN Foundation is a not for profit organisation and independently supported by the Dutch Government. Important data became available by Mesa et al. on the full spectrum of complaints related to the MPNs Essential Thrombocythemia (ET), Polycythemia Vera (PV) and Myelofibrosis (MF) and on the impact of these MPN diseases on the quality of life, social activity and work participation [2]. The Dutch MPN Patient Foundation conducted a similar survey in 2007 and 2009 among MPN patients being a member of the Dutch MPN Foundation [3-5]. The MPN Patient Foundation has its own MPN-magazine PUR SANG to inform the MPN patient's members independently from MPN doctors and specialist [5]. The Medical Advisory Board members of the MPN Foundation continuously provide the MPN Foundation patient members detailed information on signs and symptoms, diagnostic criteria and treatment recommendations by means of MPN Doctors and Patients Brochure in the Dutch and English language [1].

**Keywords:** Essential thrombocythemia; Polycythemia vera; Myelofibrosis; Constitutional symptoms; Myelproliferative neoplasms; Thrombosis burden; Fatigue; Hydroxyurea; Interpheron

## Methods

Anno 2007, the Dutch MPN Foundation had a total of 552 patient members. A written questionnaire was sent to 516 MPN patients members concerning primary symptoms including fatigue, physical mobility, social activity and work participation. In addition information was acquired regarding the diagnosis ET, PV and MF, the JAK2V617F mutation status, treatment and adverse reactions anno 2007 [3]. This survey was completed by 363 MPN patients.

Anno 2010, the Dutch MPN Foundation had nearly 700 MPN patient members. A written questionaire was sent to 624 MPN patient members concerning symptoms, treatment, physical mobility, social activity and labour participation [4]. A subgroup of respondents was selected for an additional digital questionaire containing two validated fatigue measurement instruments: the Brief Fatigue Inventory (BFI) as used by Mesa et al. [2] and the Multidimensional Fatigue Invetrory (MFI-20). This survey was completed by 450 MPN patients.

## Results

The first survey was completed in 2008 by 363 MPN patients, resulting in a 70% response rate (mean age 59 years, women 56% (n = 204): ET patients 34% (n = 123), PV patients 52% (n = 190) and MF patients 14% (n = 50) [3]. The JAK2V617F mutation status anno 2007 was assessed in 43% (n = 157) of MPN patients (n = 34 ET, n = 66 PV,

n = 8 MF). The JAK2V617F PCR test was positive in 59% of ET, 94% of PV and 44% of MF patients. Interestingly, a considerable number of patients reported vague symptoms, such as headache with or without visual impairments, dizziness and tinnitus (Figure 1), which may have led to a delay in diagnosis of MPN.

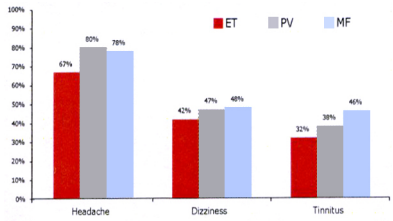


**Figure 1:** Clinical symptoms of headache with or without visual disturbances, dizziness and tinnitis in the questionaire of 363 Dutch MPN patients subdivided in 123 ET, 190 PV and 50 MF.

The main primary symptoms were fatigue, night sweats, pruritis and bone pain (Figure 2). The numbers are in accordance with those reported by Mesa et al. [2]. Indeed, in 34% of patients MPN diagnosis was initially not considered. MPN diagnosis was based on symptoms in 56% (n = 203), detected by coincidence in 30% (n = 110) and based on complications in 14% (n = 49) [3]. Mean age of diagnosis was 53 years.

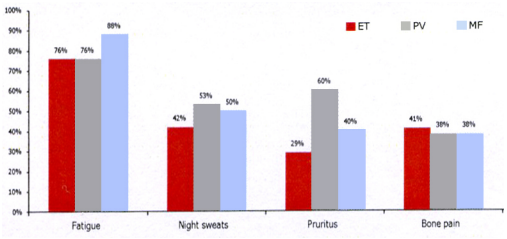


**Figure 2:** Frequency of fatigue, night sweats, pruritis and bone pain in the questionaire of 363 Dutch MPN patients subdivided in 123 ET, 190 PV and 50 MF.

Treatment modalities of the three MPNs ET, PV and MF was recorded as graphed in Figure 3. Remarkably, pruritis reported by 53 (n=193) of MPN patients was only treated in 31% (n = 60) of these patients, being efficient in only 47% (n = 28). Most applied anti-pruritic agents included alpha-interferon (14%), hydroxyurea (11%) and light therapy (PUVA) (11%). Adverse drug reactions mostly occurred in patients using hydroxyurea (n = 53, 42%) and interferon-alpha (n = 42, 33%).

These adverse reactions mainly included cutaneous and mucosal complaints, nausea and fatigue for hydroxyurea, and flu-like symptoms, fatigue and depression for interferon-alpha [3].

Physical mobility, ability to exercise and social activity was limited in many MPN patients as compared to the patient's situation before the diagnosis of MPN (Figure 4). Importantly, 37% (n = 86) of non-retired MPN patients was incapable to work full-time due to their MPN disease.

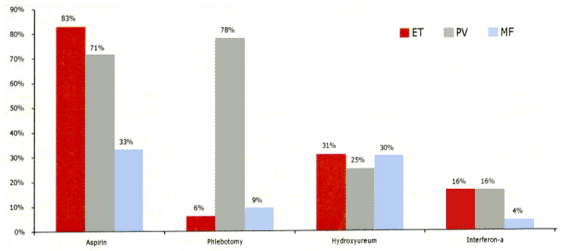


**Figure 3:** Treatment with aspirin, phlebotomy, hydroxyurea and pegylated interferon in the questionaire of 363 Dutch MPN patients subdivided in 123 ET, 190 PV and 50 MF.

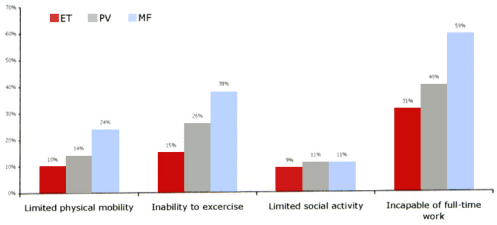


**Figure 4:** Frequency of limited physical mobility, inability to excercise, limited social activity and incapable of full-time work in the questionaire of 363 Dutch MPN patients subdivided in 123 ET, 190 PV and 50 MF.

**Brief Fatigue Inventory (BFI) and Multidimensional Fatigue Index (MFI-20) scores**

| **BFI** | **Without treatment n=19** | **Before treatment n = 211** | **During treatment n = 211** | |
|---|---|---|---|---|
| General activity | 4.68 | 3.99 | 4.84 | |
| Mood | 4.69 | 3.91 | 4.35 | |
| Walking ability | 4.5 | 3.51 | 4.35 | |
| Normal work | 4.33 | 4.83 | 4.74 | |
| Social contacts | 4.69 | 3.61 | 3.96 | |
| Joy in life | 4.14 | 3.72 | 3.98 | |
| **MFI-20** | **MPD n = 214** | **ET n = 84** | **PV n =106** | **MF n = 24** |
| General Fatigue | 13.69 | 14.46 | 14.99 | 15.68 |
| Physical fatigue | 12.67 | 13.02 | 14.08 | 14.79 |
| Reduced activity | 11.8 | 12.29 | 13 | 13.7 |
| Reduced | 10.74 | 11.38 | 11.82 | 11.93 |

**Table 1:** The mean BFI score for MPD patients during treatment.

**The second survey was completed in 2010** by 450 MPN patients, resulting in a 72% response rate (mean age 59 years, women 56% (n = 252): ET 39% (n = 157), PV 47% (n = 213), MF 14% (n = 62) [4]. The

main primary symptom was fatigue in ET 68% (n = 116), PV 91% (n = 192) and MF 92% (n = 62). BFI and MFI-20 fatigue values were obtained for a subgroup of 257 MPN patients randomly selected from the MPN population (Table 1) [4]. This subgroup contained of 36% ET (n = 98), 45% PV (n=107) and 15% MF (n = 36) patients.

Importantly to mention is that 94%, 99% and 67% of those ET, PV and MF patients were under treatment at the time of completing the additional fatigue survey. The MPN patients were limited in physical mobility in 10%, 14% and 24% of ET, PV and MF patients respectively. As compared to the situation of patient's situation before the diagnosis of MPN, the ability to exercise was limited in 15%, 29% and 38% of ET, PV and MF patients respectively. Social activity was restricted on 9%, 11% and 11% of ET, PV and MF patients respectively. Importantly, 37% of non-retired MPN patients experienced self-reported fatigue as the main reason for the inability to work full-time (ET 31%, PV 40%, MF 59%).

The mean BFI score for MPD patients during treatment was 4.81. Disease specific BFI scores for ET, PV and MF under treatment were 4.5, 5.0 and 5.5 respectively. These results are in line with previous research by Mesa et al. in which MF patients score 5.4. The mean MFI-20 General Fatigue Index score for MPD patients ET, PV and MF was 14.8, which is higher compared to 13.69 in the period before or without treatment in 214 MPD patients. All relevant fatigue values appeared to peak during treatment, compared to the period before treatment or without treatment indicating that fatigue alone is not an indication to treat MPN. The lower table shows the BFI and MFI-20 scores in perpective of other hematological diseases and healthy controls [4].

The mean BFI score in Figure 5 for MPN patients under treatment was 4.81. Disease adjusted BFI score for ET, PV and MF patients under treatment were 4.5, 5.0 and 5.5 respectively. These results are in line with previous research my Mesa et al. [2].

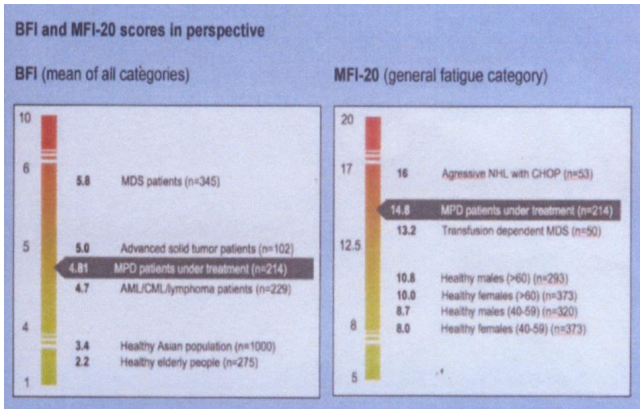


**Figure 5:** Mean Brief Fatigue Inventoty (BFI) scores for MPD (MPN) patients and Multidimenial Fatigue Index (MFI-20) [2] before, during and without treatment in a subgroup of MPN patients.

In that study the BFI score for MF patients was 5.4. The mean MFI-20 score for MPN patients under treatment was 14.8. Interestingly, all relevant fatigue values appeared to peak during treatment, compared to the period before treatment or without treatment.

## Clinical symptoms, diagnosis and treatment of ET, PV and MF in 497 MPN patients anno 2010

### Diagnosis

Since 2003, diagnosis of the MPDs followed the European Clinical and Pathological (ECP) criteria for ET, PV and MF [9]. The results of the MPN Questioaires published in PUR SANG anno 2010 were based on 497 filled forms by 271 females (54%) and 212 males (43%), mean age at diagnosis 57 years (range 20 to 84 years) [5]. The 497 MPN patients were diagnosed according to Dutch recommendations [6-9] as ET in 181 (36%), PV in 244 (50% of whom 18 as ET/PV), MF in 67 (13%), and MPN unclassifiable in 5 (1%). The primary diagnosis in 115 Dutch and Belgian hospitals was based on specific MPN related complaints in 55%, coincidental (eg routine laboratory investigation for other reasons) in 30% and after disease specific complications had occurred in 15%. Diagnosis of MPN was confirmed by bone marrow aspiration from the sternum in 235, bone marrow biopsy from the iliac crest in 475 and both in 50%. Red Cell Mass (RCM) measurement to diagnose PV and to distinguish ET from PV was performed in 31%.

PCR test for the $JAK2^{V617}$ mutation was performed in 230 (46%) MPN patients and found positive in 74% (ET n = 52, PV n = 103, MF n = 14) and negative in 26%. Sixty percent of ET, 91% of PV and 52% of MF patients were JAK2V617F positive, thereby confirming the data in the literature. After primary diagnosis 144 (25%) MPN patients (ET n = 38, PV n = 49, MF n = 27) were referred for a second opinion. The second expert evaluation led to a change in diagnosis in 8% and a change in treatment in 28% (n = 29). The second treatment option in 29 (28%) proved to be superior to the initial treatment. A change of diagnosis during follow-up occurred in 60 MPN patients, from ET into PV in 16 (9% of PV), from PV into MF in 15 (6% of PV), and from ET into MF in 10 (6% of ET).

### MPN related signs and symptoms

Based on the Dutch MPN questionaire including 36 questions to answer the top 20 complaints at time of diagnosis in 399 out of 497 (81%) MPN patients is shown in Table 2 [6-9]. The most frequent complaint is fatigue (81%) equally high in ET, PV and MF patients. Apart from variable severity of fatigue a specific pattern of signs and symptoms could be retrieved by the Dutch MPN questionaire. The signs and symptoms in ET are mainly featured by tingling and prickling sensations in footsoles, handpalms, toes and finger [9,10], cognitive concentration and visual disturbances [7]. PV patients presented with similar signs and symptoms but on top of that both itching (PV 58% vs ET 30%) and fatigue were much more prominent in PV.

A second most frequent complaint were various degrees of night sweats related to splenomegaly in about half of the MPN patients (Table 2). About one third of MPN patients suffered from bone pain (Table 2). MF patients suffered more frequently from constitutional symptoms of prominent fatigue and night sweats related to pronounced splenomegaly.

Before the diagnosis was made in 497 MPN patients, the complaints were ascribed by doctors in 173 (35%) patients to other causes including stress, burned out or overstrained in 41 (24%), to depression or hystery in 14 (8%), migraine of unknown origin in 13 (8%) and to rheuma, hypertension or fibromalgia in a few [5].

| Symptom | Top 20 MPN complaints | MPN | MPN 497 | ET 181 | PV244 | MF 67 |
|---|---|---|---|---|---|---|
| | | N=497 | % | % | % | % |
| 1 | Fatigue, listless | 399 | 81 | 80 | 81 | 85 |
| **2** | **Microvascular acra [6]** | **278** | **57** | **61** | **56** | **46** |
| **3** | **Cognitive Disturbances [7]** | **262** | **53** | **52** | **56** | **45** |
| **4** | **Visual disturbances [7]** | **249** | **51** | **50** | **52** | **46** |
| 5 | Night sweats | 236 | 48 | 44 | 50 | 52 |
| 6 | Itching | 220 | 45 | 30 | 58 | 36 |
| 7 | Dizziness | 218 | 44 | 44 | 46 | 39 |
| 8 | Bruises, bleedings | 211 | 43 | 40 | 45 | 43 |
| **9** | **Splenomegaly constitutional symptoms** | **198** | **40** | **22** | **43** | **78** |
| 10 | Tinnitus | 188 | 38 | 38 | 39 | 37 |
| 11 | Migraine headache without visual symptoms | 184 | 37 | 46 | 35 | 22 |
| 12 | Bone pain | 172 | 35 | 33 | 36 | 34 |
| 13 | Heart arrythmias | 154 | 31 | 34 | 31 | 24 |
| 14 | Dysarthria, dyslexia, | 151 | 31 | 31 | 31 | 30 |
| 15 | Hypersensitive to sounds and noices | 149 | 30 | 29 | 32 | 28 |
| 16 | Paleness | 145 | 29 | 30 | 26 | 40 |
| 17 | Claudicatio intermittens | 140 | 28 | 28 | 30 | 24 |
| 18 | Hypersensitive to lights | 136 | 28 | 25 | 32 | 16 |
| 19 | Visual disturbances without headache | 18 | 33 | 54 | 3 | 90 |
| 20 | Headache without visual symptoms | 24 | 43 | 43 | 4 | 90 |

Microvascular acra: Tingling,prickeling sensations, redness,swelling and/or bluish discolouration of footsoles, handpalms, toes and/or fingers [6].

Cognitive disturbances of concentration and memory and sudden attacks of unconscienceness.

Visual disturbances of scintillating scotomas, light flashes, blurred vision, transient monocular blindness, rapid spreading of visual figure disturbances [7].

Attacks of migraine-like headaches followed by nausea or vomiting or loss of consciencenous or transient paresis of one extremity [7].

**Table 2:** Top 20 clinical manifestations in 497 patients with who defined myeloproliferative neoplasm (MPN) 181 essential thrombocythemia (ET) 244 polycythemia vera (PV), and 67 myelofibrosis ( MF0 patients based on the Dutch MPN Questionaire 2009-2011 [5].

## Treatment and adverse reactions

Treatment in 497 MPN patients was started with low dose aspirin or calcium carbasalate (Ascal) in 70% and phlebotomy in 42% (mainly PV 91%), hydroxyurea in 29%, and pegylated interferon-alpha2a in 7%, wait and see in 8% (n = 42 of whom 26 with MF) of MPN patients at time of diagnosis [5]. The treatment changed during follow-up in 294 (60%) of MPN patients: ET in 64% (n=115), PV in 59% (n = 143) and MF in 49% (n = 33).

Out of 459 evaluable adverse drug reactions or side effects were recorded in one third (35%) of MPN patients: HU in 41% (n = 69), IFN in 28% (n = 47) of all side effects. Most frequent side effects of HU were skin and mucocutaneous complaints including dry skin, skin lesions, skin ulcers, itching, skin carcinoma, brittle nails, aphtous ulcers and hair loss [5].

Most frequent side effects of IFN were flu-like symptoms, fatigue and mood disturbances [5]. Low dose aspirin or Ascal induced gastritic complants in 11% for which treatment with metronazol was usually indicated [5].

## Work participation, mobility and social activity [5]

Out of 497 MPN patients 168 (34%) indicated not to be able anymore to participate in their job. Out of 318 MPN patients who still wish to work 18% were completely and 14% partially unable to work as the consequence of MPN disease.

As the consequence of their disease, about one fourth of MPN patients are restricted in their activities to walk in 24% (n = 117), to bicycle in 22% (n = 111), or sports in 24%, (n = 117). Out of 497 MPN patients 86% could accept their MPN disease to live with it themselves (78%) by compassion from families and friends in 41% and professional help was given in 12%. In 46 (9%) patient MPN disease was a great suffer and nearly impossible to live with.

## Discussion

The Dutch MPN Patient Foundation conducted two questionaire surveys among MPN patients in The Netherlands and Belgium on the impact of fatigue related to MPN on the quality of life, social activity and labour participation. In a cohort of 450 MPN patients subdivided in 157 ET, 213 PV and 62 MF patients, they found a high impact of MPN disease-related fatigues on daily activities and labour participation, especially during treatment.

In the light of the chronic nature of treatment of MPN patients, this justifies that prospective unmet need (PUN) studies are warranted in which the effect of treatment with aspirin, phlebotomy/aspirin, pegylated interferon, anagrelide, hydroxyurea and JAK2 inhibitors in ET, PV and MF patients of various molecular etiology (Table 3) should be evaluated not only directed towards clear indications and efficacy of the non-leukemogenic agents in particular, but that the effects on fatigue, quality of life and labour participation should be incorporated as well [9-10].

The treatment efficacy should not only be defined as the capacity to decrease thrombosis and hemorrhages, but should also include the capacity to reduce mutation allele burden and myeloproliferative disease burden and the effects on quality of life and work paticipation as well.

Because of advanced or symptomatic MPN disease burden, 31% of ET, 29% of PV and 30% of MF were on treatment with hydroxyurea and 16% of ET and PV and 4% of MF were on treatment with peglyated interferon (Pegasys$^{R}$). In the Italian study of Vannucchi et al. [12], a total of 214 patients were treated with phlebotomy, 58% of 219 PV and 4% of 257 ET patients.

Myelosuppressive chemotherapy was administered to 497 patients (52%) including 59% of 219 PV and 48% of 257 ET patients. The 20% difference of HU use (50% of Italian MPN-T patients versus 30% of Dutch MPN-T patients) can readily be ascribed to significant differences in the Italian versus the Dutch guidelines for ET and PV patients.

MPN patients in the Netherlands were treated according to the 2000 guidelines for ET and PV [9]. Low risk MPN disease in ET and PV patients at ages 18 to 80 years is defined by platelet count <1500 × $10^9$/L, absence of vascular risk factors like hypertension, hypercholesterolemia, diabetes atherosclrosis and absence of bleeding complications.

First line treatment option in MPN-T disease in ET and PV patients followed the published Dutch guidelines since 2000 [9]. If asymptomatic, no microvascular symptoms and no major thrombosis like minor stroke of myocardial infarction low dose aspirin 40 mg a day is given in JAK2$^{V617F}$ mutated MPN-T.

Symptomatic MPN patients including microvascular circulation disturbances including migraine atypical TIAs, minor TIAs, low back pain, pain-full toes or fingers, but no major thrombosis were treated low dose aspirin.

When MPN is associated with leukocytosis, moderate splenomegaly or platelet count above 1000×$10^9$/l low dose Pegasys 45 ug/ml every two weeks or once per week is the first line treatment option in JAK2V617F mutated ET and PV. At age above 70 freedom to choose hydroxyurea or low dose pegasys must prevail. Please note that these are general Dutch MPN-T treatment guidelines, which has to be discussed with your local hematologist or internist for approval.

The WHO-ECMP criteria clearly define and stage the JAK2$^{V617F}$ defined MPN entity of prodromal PV, prefibrotic PV, early fibrotic PV, PV complicated by myelofibrosis (post-PV MF), significant myeloid metaplasia of the spleen with splenomegaly and related constitutional symptoms (Table 3) [9,10].

Within the JAK2$^{V617F}$ MPN phenotypes, the JAK2$^{V617F}$ mutated hypercellular ET is associated with clustered pleiomorphic megakaryopoiesis, increased granulopoiesis and relative decrease of erythropoiesis without a documented history of ET or PV.

The WHO-CMP criteria for staging of the JAK2 MPN phenotypes have important implications in choosing proper targeted treatment options for the prevention of thrombotic and bleeding complications in prodromal PV and PV and for the management of serious complications of progressive MPN disease burden requiring myeloreductive treatment with peglyated interferon (PegasysR) and if non-responsive or side effects low dose hydroxyurea to correct increased blood cell counts in overt and advanced PV patients (Table 3)[10].

Venesection aiming at a hematocrit below 0.45 in males and below 0.42 in females is the first line treatment option in PV patients [10]. Phlebotomy aiming more strictly at a hemotocrit of less than 0.40 and a MCV of less than 70 fl in males and females on top of well controlled low dose aspirin in PV patients will reduce the cumulative incidence of minor and major thrombosis from above 50% to less than 2% per 100 patient/years during long-term or life-long follow-up, but the microvascular syndrome of associated thrombocythemia persist [9,10].

According to current insights, low dose interferon is the treatment of choice in intermediate stage PV patients (Table 3) [9,10]. If not responsive to IFN or side effects induced by IFN, hydroxyurea is the second line myelosupressive treatment option in JAK2$^{V617F}$ mutated ET and PV patients (Table 3).

Hydroxyurea is not an innocent drug and should be used with caution and withheld as long as phlebotomy and low dose aspirin are effective in the treatment of early and intermediate plethoric PV stages 1and 2 (Table 2). The final analysis of the 1980 French PVSG study of HU as the upfront first-line therapy in 136 evaluable PV patients younger than 65 years is published in 2011 [12,13]. The cumulative incidence (probability) of myelofibrosis (MF) at 10, 15 and 20 years was 15%, 24% and 32% in the HU arm and the cumulative incidence of AML/MDS at 10, 15 and 20 years was 7.3, 10.7% and 16.6% for HU treated PV patients. Proper staging of PV in terms of JAK2$^{V617F}$ mutation load, and MPN disease burden by measuring the degree of splenomegaly and severity of constitutional symptoms including itching on top of bone marrow histology and grading of fibrosis is of huge importance since it has significant implications for a non-leukemogenic or the least potential leukemogenic treatment options in low, intermediate and high risk PV patients (Table 3) [9].

| **WHO-CMP PV stage** | **0** | **1** | **2** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|---|---|---|
| **WHO-CMP** | Prodromal | Erythrocy-themic PV | Early PV Classical PV | Manifest PV | **Hyperproliferative PV à** | **Inapparent** | **Spent PV** |
| Clinical Diagnosis | PV | | | Classical PV | **Masked PV** | **PV MF Masked PV** | **Post-PV MF** |
| LAP-score | ↑ | ↑ | ↑ | ↑ | ↑/↑↑ | ↑ | variable |
| EEC | + | + | + | + | + | + | + |
| Serum EPO | N/↓ | N/↓ | ↓ | ↓ | ↓ | ↓ | variable |
| Erythrocytes $x10^{12}$/l | >5.8 | <5.8 | >5.8 | >5.8 | Around 5.8 | **Normal <5.5** | **Decreased** |
| Leukocytes $x10^{9}$/l | <12 | Below 12 | Above 12 | < or->15 | >20 | N or ↑ | >20 |
| Platelets $x10^{9}$/l | Above 400 | Below 400 | Around 400 | Above 400 | < or >1000 | N low or ↑ | variable |
| WHO-CMP bone marrow | Early PV | Early PV | Early PV | Trilinear PV | Trilinear PV | Trilinear PV | Myelofibrosis |
| Bone marrow cellularity (%) | 50-80 | 50-80 | 60-100 | 80-100 | 80-100 | 60-100 | Decreased |
| Grading reticulin fibrosis: RF | RF 0-1 | RF 0-1 | RF 0-1 | RF 0/1, | RCF1/2/3 | RCF 1/2/3 | RCF 3/ 4 |
| Grading myelofibrosis: MF | MF 0 | MF 0 | MF 0 | MF 0 | MF 0/1 | MF 0/2 | MF 2/3 |
| Splenomegaly grading | | | | | | | |
| Spleen size, echogram cm | <12-15 | <13 | Dec-15 | Dec-16 | 18->20 | 16 >20 | >20 |
| Spleen size on palpation cm | 0-3 | NP | 0-3 | 04-Jun | >6 | >6 | >8 |
| $JAK2^{V617F}$ in Granulocytes % | low | low | Moderate <50 | High >50 | High >50 | Mod/High | High >50 |
| $JAK2^{V617F}$ in BFU-e (exon 12) | +(++) | +(++) | +(++) | ++ | ++ | + | ++ |
| Risk stratification 2014 ? | Low risk | Low risk | Low risk | Intermediate risk PV | High risk | High Risk PV | Post-PV MF |
| Therapeutic implications | | | | | PV early MF | Inapparent PV | Spent PV |
| First line Aspirin/ Phlebotomy | Aspirin | Aspirin | Phlebotomy | Phlebotomy* | If IFN resistant à | JAK2 | JAK2 |
| Second line IFN versus | Phlebotomy | Phlebotomy | Aspirin | Aspirin | HU or JAK2 | Inhibitor First line | Inhibitor à |
| Hydroxyurea (HU) | | | Low dose IFN ? responsive | IFN ? resistant ? HU | inhibitor | | Bone marrow |
| Third line JAK2 inhibitor | | | | | | | transplant |

*↑ = increased, ↓ = decreased, N = normal, + = present or heterozygous; ++ = homozygous

**Table 3:** Staging of $JAK2^{V617F}$ mutated prodromal PV, erythrocythemic PV, classical PV, masked PV, early PV-MF, inapparent PV, spent phase PV and post-PV myelofibrosis (MF) according to 2014 WHO-CMP criteria for staging of PV related to therapy [10].

As shown in Table 3, high risk PV and MF patients with advanced MPN disease in terms of high $JAK2^{V617F}$ allele burden, progressive MPN disease with splenomegaly and constitutional symptoms are candidates for myelosuppressive (hydroxyurea) or myeloreductive (JAK2 inhibitors) treatment.

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