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Myeloproliferative Neoplasm (MPN) Disease Burden, Quality of Life, Social Activity, Work Participation and Fatigue in 497 MPN Patients: A Comparison of Treatment Options in Dutch, Italian and Mayo Clinic Studies

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ABSTRACT

The main primary symptoms in 363 patients with myeloproliferative neoplasm (MPN) patients subdivided in 123 ET, 190 PV and 50 MF patients were fatigue, night sweats, pruritis and bone pain. A considerable number of MPN patients reported vague symptoms, such as headache with or without visual impairments, dizziness and tinnitus. MPN diagnosis was initially not considered in 34%. 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). Mean age of diagnosis was 53 years. 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 500 MPN patients was fatigue (N=391, 81%) equally high in ET, PV and MF patients. Forty to 60% of ET and PV patients presented with aspirin responsive microvascular disturbances mainly featured by tingling and prickling sensations in foot soles, hand palms, toes and fingers, cognitive concentration and visual disturbances. ET and PV patients presented with itching (PV 58% vs. ET 30%). Various degrees of constitutional symptoms including night sweats were related to splenomegaly in about half of ET, PV and MF patients. 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 MPN diagnosis was made the complaints were ascribed by doctors to other causes in 173 (35%) patients 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. Treatment in 497 MPN patients consisted of low dose aspirin in 70% and phlebotomy in 42% (mainly PV 91%), hydroxyurea in about 30% of ET, PV and MF and pegylated interferon-alpha-2a in 16% of ET and PV patients.

Keywords: Myeloproliferative neoplasm, Fatigue, Sweat, Patients, Diagnosis

INTRODUCTION

The Dutch MPN Patients Foundation was founded in 2003 by Connie Luteijn with the support of the medical advisory committee of Dutch Internists and MPN experts in Hematology. This foundation 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 [1-6]. The Dutch MPN Foundation is a not for profit organization and independently supported by the Dutch Government.

Important data became available by Mesa et al. [7] on the full spectrum of complaints related to the myeloproliferative neoplasms (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. We therefore conducted a similar survey in 2007 and 2009 among MPN patients being a member of the Dutch MPN Foundation. The MPN Patients Foundation has its own MPN-magazine PUR SANG to

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inform the MPN patients members independently from MPN doctors and specialists [8]. 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 [9-11].

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 presenting manifestations of MPN, vascular symptom burden and used validated instruments of fatigue, physical mobility, social activity and work participation according to Mesa et al. [7] and Mendeza et al. [8]. In addition information was acquired regarding the diagnosis ET, PV and MF, the $JAK2^{V617F}$ mutation status, treatment and adverse reactions anno 2007 [9-11]. This survey was completed by 363 (response rate 70%) MPN patients [6].

Anno 2010, the Dutch MPN Foundation had nearly 700 MPN patient members. A second written questionnaire was sent to 624 MPN patient members concerning symptoms, treatment, physical mobility, social activity and labor participation [7,8]. A subgroup of respondents was selected for an additional digital questionnaire containing two validated fatigue measurement instruments: the Brief Fatigue Inventory (BFI) as used by Mendoza et al. [8] and the Multidimensional Fatigue Inventory (MFI-20). This survey was completed by 450 (response rate 72%) MPN patients.

DIAGNOSIS: 2000-2002 ECP CRITERIA OF ET, PRODROMAL PV, PV, ET ASSOCIATED WITH CMGM/PMGM

Since 2000, diagnosis of the MPDs followed the European Clinical and Pathological (ECP) criteria for ET, PV and MF **(Figures 1 and 2)** [1-3]. The 2000 European Clinical and Pathological (ECP) criteria distinguish at least five stages of myeloproliferative neoplasm (MPN): primary MPN stage 0, essential thrombocythemia with features of latent polycythemia vera (=PV, with increased LAP score and increased erythrocythemic megakaryocytic myeloproliferation), masked PV, erythrocythemia PV and classical PV **(Figure 1)** [12-15]. Since 1980 we have used erythrocyte count above the upper limit of normal to replace red cell mass as a major criterion to distinguish classical PV from ET with features of PV (prodromal PV) (http://www.mpn-stichting.nl/doctors_brochure_2004.pdf) [3]. The bone marrow histology of "true" ET is featured by large to giant megakaryocytes with hyper lobulated stag-horn like nuclei, normal LAP score and no features of PV at diagnosis and during follow-up **(Figure 2)** [2,14]. Chronic or primary megakaryocytic granulocytic myeloproliferations (CMGM/PMGM, **Figure 2**) is the third distinct MPN of hypercellular ET due dual megakaryocytic/granuloctic myeloprliferation and relative reduction of erythropoiesis in the bone marrow featured by immature megakaryocytes with clumsy cloud-like mega karyocytes, which are not seen in ET and PV [2,14].

Diagnostic Criteria of PV by including bone marrow histopathology

Diagnostic criteria PV		*Confirmative criteria PV*	
A1	Raised red cell mass: RCM male >36 ml/kg, female >32 ml/kg	B1	Thrombocythemia platelet count $>400 \times 10^9$/l
A2	Absence of any cause of secondary erythrocytosis by clinical and laboratory investigations	B2	Granulocytes $>10 \times 10^9$/l and/or raised LAP score in the absence of fever or infection
A3	Histopathology of bone marrow biopsy:	B3	Splenomegaly on palpation or > 11 cm on ultrasound scan or CT
	a) increase and clusters of pleomorphic enlarged mega-karyocytes with hyperploid nuclei	B4	Spontaneous erythroid colony formation in the absence of Epo and low plasma Epo level
	b) increased cellularity: panmyelosis		
	c) reticulin fibers (optional)		

A1+A2+A3 is consistent with early plethoric stage of PV ("idiopathic erythrocytosis").

A2+A3+ elevated hematocrit >0.50 is consistent with latent or early plethoric stage PV.

A1+A2+A3+ any one from category B establish overt PV according to the PVSG.

A2+A3+ elevated hematocrit >0.50 + any one feature in category B plus a typical clinical picture establish overt PV without the need of red cell mass measurement.

A3 + B1 is consistent with essential thrombocythemia with features of latent PV.

A3 + B3 and/or B4 is consistent with latent PV or primary MPD

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Michiels JJ, Barbui T, Finazzi G, Fuchtman SM, Kutti J, Rain JD, Silver RT, Tefferi A & Thiele J: Diagnosis and treatment of polycythemia vera and possible future study designs of the PVSG. *Leukemia and Lymphoma* 2000; 36: 239-253

Figure 1. Diagnostic Criteria of PV by including bone marrow histopathology.

The 2000 European Clinical and Pathological (ECP) criteria distinguish at least five stages of myeloproiferative neoplasm (MPN): Primary MPN stage 0, essential thrombocythemia with features of latent polycythemia vera (=PV, with increased LAP score and increased erythrocthemic megakaryocytic myeloproliferation), masked PV, erythrocythemia PV and classical PV. Since 1980 we have used erythrocyte count above the upper limit of normal to replace red cell mass as a major criterion to distinguish classical PV from ET with features of PV (prodromal PV) [1]

Clinical Criteria		Pathological Criteria	
A1	Persistent increase of platelet count: grade I: 400-1500, grade II: >1500 × 10^9/L	B1	Predominant proliferation of enlarged megakaryocytes with hyperlobulated nuclei and mature cytoplasm, lacking conspicuous cytological abnormalities
A2	Normal spleen or only minor splenomegaly on echogram		
A3	Normal LAP score, normal ESR, and increased MPV		
A4	Spontaneous megakaryocyte colony formation (CFU-Meg)		
A5	No signs or cause of RT	B2	No proliferation or immaturity of granulopoiesis or erythropoiesis
A6	No preceding or allied other subtype of MPD, CML, or MDS		
A7	Absence of the Philadelphia chromosome	B3	No or only borderline increase in reticulin

* The combinations of A1 and B1 + B2 establish (true) ET (thrombocythemia vera). Any other criterion confirms ET. LAP indicates leukocyte alkaline phosphatase; ESR, erythrocyte sedimentation rate; MPV, mean platelet volume; CRU-Meg, colony-forming unit–megakaryocyte; RT, reactive thrombocytosis; MPD, myeloproliferative disorder; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome.

Figure 2A. The European Clinical and Pathological (ECP) criteria for true ET according to Michiels and Thiele [22].

Updated Clinicopathological Criteria for the Diagnosis of Idiopathic Myelofibrosis (IMF) or Agnogenic Myeloid Metaplasia (AMM)*

Clinical Criteria		Pathological Criteria	
A1	No preceding or allied other subtype of MPD, CML, or MDS	B1	Megakaryocytic and granulocytic myeloproliferation and relative reduction of erythroid precursors. Abnormal clustering and increase in atypical giant to medium-sized megakaryocytes containing bulbous (cloud-like) hypolobulated nuclei and definitive maturation defects.
A2	Early clinical stages		
	Normal hemoglobin or anemia, grade I: hemoglobin ≥12 g/dL		
	Slight or moderate splenomegaly on palpation or >11 cm on ultrasound scan or CT		
	Thrombocythemia, platelets >400 × 10^9/L		
A3	Intermediate clinical stage		
	Anemia grade II: hemoglobin ≥10 g/dL		
	Definitive leuko-erythroblastic blood picture and/or tear-drop erythrocytes		
	Splenomegaly		
	No adverse signs†		
A4	Advanced clinical stage		
	Anemia grade III: hemoglobin <10 g/L		
	One or more adverse signs†		

Figure 2B. The European Clinical and Pathological (ECP) criteria for prefibrotic chronic idiopathic myelofibrosis (CIMF) or primary megakaryocytic granulocytic myeloproliferation (PMGM [22]). PMGM is labeled as primary myelofibrosis (PMF) in the WHO classifications.

RESULTS

The first survey was completed in 2008 by 363 MPN patients (mean age 59 years, women 56% (n=204): ET patients 34% (n=123), PV patients 52% (n=190) and MF patients 14% (n=50) [9]. The $JAK2^{V617F}$ mutation status anno 2007 was assessed in 43% (n=157) of MPN patients (n=34 ET, n=66 PV, n=8 MF). The $JAK2^{V617F}$ 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 3A)**, which may have led to a delay in diagnosis of MPN. The main primary symptoms were fatigue, night sweats, pruritis and bone pain **(Figure 3B)**. The numbers are in accordance with those reported by Mesa et al. [7] **(Table 1 and Figures 3B and 4)**. 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) [9]. Mean age of diagnosis was 53 years.

Table 1. Comparative analysis of myeloproliferative associated symptom burden and treatment by diagnosis of the myeloroliferative neoplasms (MPN) as polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF) in the study of Mesa et al. [7] and the present study of Michiels.

Patient MPN Diagnosis	PV		ET		MF	
	Mesa	Michiels	Mesa	Michiels	Mesa	Michiels
Number of patients	405	244	304	181	456	67
Symptom burden						
Splenomegaly	42%	36%	24%	22%	56%	78%
Fatigue	85%	81%	72%	80%	84%	85%
Itching	65%	58%	40%	30%	50%	36%
Night sweats	49%	50%	41%	44%	56%	52%
Bone pain	43%	36%	41%	33%	47%	34%
Therapy						
Aspirin	72%	71%	77%	83%	49%	33%
Hydroxyurea	53%	25%	63%	31%	51%	30%
Anagrelide	22%	Near 0%	60%	Low	29%	Near 0%
Interferon	16%	16%	14%	16%	21%	4%

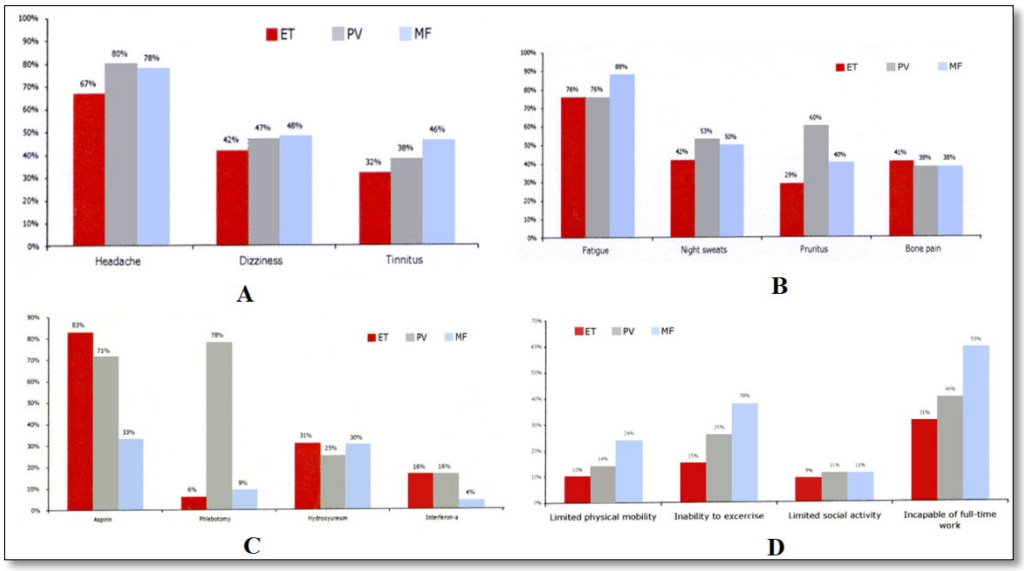

Figure 3. The spectrum of symptoms in 123 ET, 190 PV and 50 MF (363 MPN) patients as derived from a questionnaire of 36 questions on behave of the Dutch MNP Patients Foundation 2003-2010. A. Clinical symptoms of headache with or without visual disturbances, dizziness and tinnitis in the questionnaire of 363 Dutch MPN patients subdivided in 123 (34%) ET, 190 (52%) PV and 50 (14%) patients [6]. B. Frequency of fatigue, night sweats, pruritis and bone pain in the questionnaire of 363 Dutch MPN patients subdivided in 123 (34%) ET, 190 (52%) PV and 50 (14%) patients [6]. C. Treatment with aspirin, phlebotomy, hydroxyurea and pegylated interferon in the questionnaire of 363 Dutch MPN patients subdivided in 123 ET, 190 PV and 50 MF. D. Frequency of limited physical mobility, inability to exercise, limited social activity and incapable of full-time work in the questionnaire of 363 Dutch MPN patients subdivided in 123 ET, 190 PV and 50 MF.

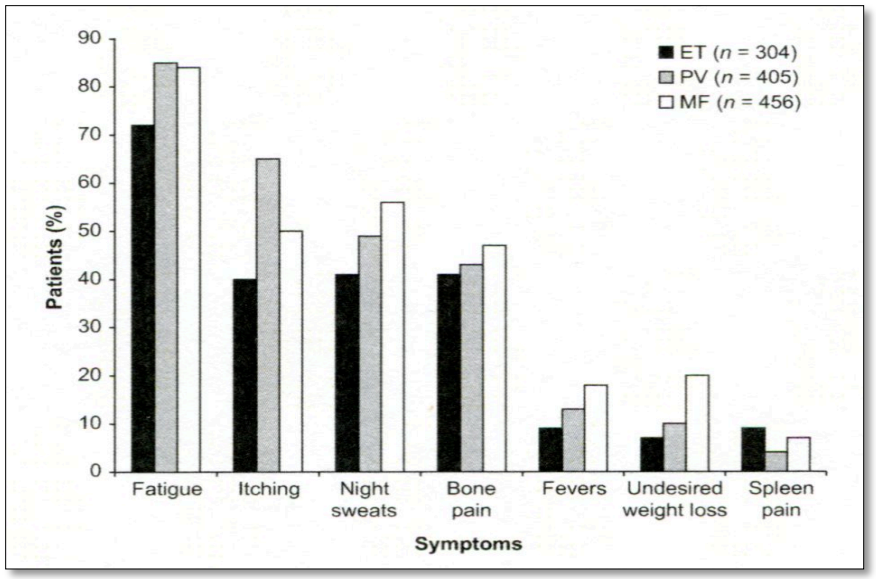

Figure 4. Frequency of fatigue, itching (pruritis) , night sweats, and bone pain in the questionnaire of 1165 MPN patients from the study of Mesa et al. [7], 24 subdivided in 304 (26%) ET, 405 (35%) PV and 456 (39%) patients in the setting of six participating academic hematology/oncology departments including the Mayo Clinic Rochester and Scottsdale, MD Anderson Cancer Center Houston and Dana Farber Cancer Institute Boston.

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

(n=42). These adverse reactions mainly included cutaneous and mucosal complaints, nausea and fatigue for hydroxyurea and flu-like symptoms, fatigue and depression for interferon-alpha [9]. 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 3D)**. Importantly, 37% (n=86) of non-retired MPN patients was incapable to work full-time due to their MPN disease.

Brief Fatigue Inventory (BFI) and Multidimensional Fatigue Index (MFI-20) fatigue values were obtained for a subgroup of 257 MPN patients randomly selected from the MPN population **(Figure 5)** [10]. 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 retricted 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 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. [7]. 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 **(Figure 5)**. Interestingly, all relevant fatigue values appeared to peak during treatment, compared to the period before treatment or without treatment **(Figure 5)**.

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	11.80	12.29	13.00	13.70
Reduced	10.74	11.38	11.82	11.93

Figure 5. Mean BFI scores for MPN patients before, during and without treatment of MPN patients irrespective of MPN disease burden [10].

Interpretation: The mean BFI score for MPN 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. [7] in which MF patients score 5.4. The mean MFI-20 General Fatigue Index score for MPN patients ET, PV and MF was 14.8, which is higher compared to 13.69 in the period before or without treatment in 214 MPN 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 perspective of other hematological diseases and healthy controls [10].

CLINICAL SYMPTOMS, DIAGNOSIS AND TREATMENT OF ET, PV AND MF IN 497 MPN PATIENTS ANNO 2010

Since 2003, diagnosis of the MPNs followed the European Clinical and Pathological (ECP) criteria for ET, PV and MF [1-6,12-15]. The second survey was completed in 2010 by 450 MPN patients (women 56%), resulting in a 72% response rate: ET 39% (n=157), PV 47% (n=213), MF 14% (n=62) [11]. The results of the MPN Questionaries' 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) [11]. The 497 MPN patients were diagnosed according to Dutch recommendations [12-15] 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 (e.g. 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 and bone marrow biopsy from the iliac crest in 475 (96%). 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 $JAK2^{V617F}$ positive, thereby confirming the data in the literature [14]. 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 questionnaire including 36 questions to answer the top 20 complaints at time of diagnosis in 399 out of 497 (81%) MPN patients are shown in **Table 2**. 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 questionnaire. The signs and symptoms in ET are mainly featured by tingling and prickling sensations in foot soles, hand palms, toes and fingers [16-20], cognitive concentration and visual disturbances [19,20]. Itching in PV (58%) and ET (30%) and fatigue were much more prominent in PV. Various degrees of night sweats related to splenomegaly occurred 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 (78%) related to pronounced splenomegaly **(Table 2)**.

Table 2. Top 20 clinical manifestations in 497 patients with who defined myeloproliferative neoplasm (MPN) 181 (36%) essential thrombocythemia (ET) 244 (49%) polycythemia vera (PV) and 67 (14%) myelofibrosis (MF with hemoglobin <12 g/dL = PMGM intermediate or advanced stage) patients based on the Dutch MPN Questionnaire 2009-2011 [8].

Symptoms	Top 20 MPN complaints	MPN	MPN 497	ET 181	PV 244	MF 67
		N=497	% of 497	% of 181	% of 244	% of 67
1	Fatigue, listless	399	81	80	81	85
2	*Microvascular acra erythromelalgia*	278	57	61	56	46
3	*Cognitive disturbances*	262	53	52	56	45
4	*Visual disturbances*	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 noises	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, erythromelalgia: Tingling, prickling sensations, redness, swelling and/or bluish discoloration of foot soles, hand palms, toes and/or fingers [16,17]

Cognitive disturbances of concentration and memory and sudden attacks of unconsciousness [18]

Visual disturbances of scintillating scotomas, light flashes, blurred vision, transient monocular blindness, rapid spreading of visual figure disturbances [18,19]

Attacks of migraine-like headaches followed by nausea or vomiting or loss of consciousness or transient paresis of one extremity [18,19]

Before the MPN diagnosis was made the complaints were ascribed to myeloproliferative disease ET, PV or MF 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 [11].

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

WORK PARTICIPATION, MOBILITY AND SOCIAL ACTIVITY [11]

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. Collection and analysis of results derived from the Dutch MPN questionnaire 2011 (available at: http://www.mpn-stichting.nl and info@mpn-stichting.nl) by the Dutch MPN Foundation is a continuous process.

DISCUSSION AND CONCLUSION

In the cohort of 450 MPN patients subdivided in 157 ET, 213 PV and 62 MF patients, we found a high impact of MPN disease-related fatigues on daily activities and labor 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 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 labor participation should be incorporated as well. 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 MPN disease burden and the effects on quality of life and work participation as well. In the survey of 363 MPN (123 ET, 190 PV and 50 MF) patients 93% of PV, 71% of ET and 37% of MF were on aspirin mainly because of microvascular symptoms including migraine-like headache, acral paresthesia, erythromelalgia, transient neurological and visual disturbances. Phlebotomy became the first line treatment in 6% of ET, 78% of PV and 9% of MF. Because of advanced or symptomatic MPN disease 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 2007 study of Mesa et al 50 to 60% of ET and PV patients were on hydroxyurea therapy **(Table 3) [**7]. In the Italian study of Vannucchi et al. [21], 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 USA and Italian ET/PV patients versus 30% of Dutch ET/PV patients) can readily be ascribed to significant differences in the USA/Italian versus the Dutch guidelines for MPN-T disease in ET and PV patients [13-15]. Low risk 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 in ET and PV patients followed the published Dutch guidelines since 2000 **(Table 4)**. If asymptomatic, no micricovascular symptoms and no major thrombosis like minor stroke of myocardial infarction low dose aspirin 40 mg a day is given in JAK2^{V617F} mutated thrombocythemia MPN (MPN-T) patients. Symptomatic MPN-T patients including microcrovascular circulation disturbances including migraine atypical TIAs, minor TIAs, low back pain, painful toes or fingers, but no major thrombosis was treated low dose aspirin. When MPN-T is associated with leukocytosis, moderate splenomegaly or platelet count above 1000 × 10^9/l low dose Pegasys 45 ug/ml will become the treatment of choice in JAK2^{V617F} 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.

Table 3. Work participation and mobility restriction in MPN patients.

Number of evaluated MPN patients		**497**	**100%**
Unable to work		168	34%
	Completely unable to work		18%
	Partially unable to work		14%
Restricted in their activities		117	24%
	Restricted to bicycle		22%
	Restricted to sport		24%
MPN disease 'a great suffer		46	9%

Table 4. Dutch treatment recommendation for the use of aspirin and platelet reduction in thrombocythemia of ET and PV patients with low MPN disease burden: no or slight splenomegaly (<14 cm on echogram), no or minor increase of Leukocytes (<15 × 10^9/L) no or minor itching, no constitutional symptoms and normal LDH [1,16].

Risk category	**Platelet number, age and risk**	**Treatment option**
	Platelet number 400-1000 × 10^9/L	Low dose aspirin 75 mg OD
Low	Age 18 to >80 years	Calcium carbasalate 100 mg OD
	No microvascular events, no bleedings	
	No cardiovascular risk factors	
Low-Intermediate	Platelet number 400-1000 × 10^9/L	Low dose aspirin 75 mg OD
	Age 18 to >80 years	Calcium carbasalate 100 mg OD
	Microvascular manifestations	If platelet counts above 1000 × 10^9/L
	No major thrombosis, no bleedings	and minor or significant bleeding
	No cardiovascular risk factors	Platelet reduction by ana, IFN or HU
Intermediate-High	Platelet number 400-1000 × 10^9/L	Low dose aspirin or Calcium carbasalate
	Age 18 to >80 years	Consider platelet reduction
	Presence of cardiovascular risk factors	Anagrelide, IFN or HU
High	Platelet number above 1000 × 10^9/L	Platelet reduction from above 1000 to
	Age 18 to >80 years	below 1000 × 10^9/L with ana, IFN or HU
	Bleeding at platelets >400 × 10^9/L	Aspirin at platelets below 1000 × 10^9/L

OD: Once Daily; ana: anagrelide; IFN: Pegylated Interpheron-Alpha; HU: Hydroxyurea

At platelet count between 1000 and 1500 × 10^9/L when on aspirin for microvascular manifestation's the risk of bleeding is increased. If bleeding is present reduction at platelet count by anagrelide or IFN from values above to below 1000 × 10^9/L is recommended. HU is indicated if case rapid reduction of high to very high platelet count is indicated. Symptomatic ET with features of PV, splenomegaly and leukocytosis (masked PV or post-ET MF) treatment with low dose IFN is indicated. If non-responsive to IFN or side effects consider hydroxyurea.

The 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 5)** [22,23]. Within the $JAK2^{V617F}$ MPN phenotypes, the $JAK2^{V617F}$ mutated hypercellular ET is associated with clustered pleomorphic megakaryopoiesis, increased granulopoiesis and relative decrease of erythropoiesis without a documented history of ET or PV. The integrated

WHO-CMP criteria surely will 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 myloreductive treatment with peglyated interferon (Pegasys^{R}) and if non-responsive or side effects low dose hydroxyurea to correct increased blood cell counts in overt and advanced PV patients [10,13]. 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. 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 significantly reduce the cumulative incidence of major thrombosis, but the microvascular syndrome of associated thrombocythemia persist [13]. According to current insights, low dose interferon is the treatment of choice in intermediate stage PV patient [15,22,23]. 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 5)**. Hydroxyurea is not an innocent drug and should be used with caution. 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 5)**. As shown in **Table 5**, high risk PV and MF patients with advanced MPN-T 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 [24].

Table 5. Staging of JAK2^{V617F} mutated prodromal PV, erythrocythemic PV, classical PV, early MF, in apparent PV, spent phase PV and post-PV myelofibrosis (MF) according to 2014 WHO-CMP criteria for staging of PV related to therapy [1,16-23].

WHO-CMP PV stage	**0**	**1**	**2**	**3**	**4**	**5**	**6**
WHO-CMP Clinical Diagnosis	Prodromal PV	Erythrocy-themic PV	Early PV Classical PV	Manifest PV Classical PV	Hyper proliferative PV → Masked PV	Advanced PV MF Masked PV	Spent PV Post-PV MF
LAP-score	↑	↑	↑	↑	↑/↑↑	↑	variable
EEC	+	+	+	+	+	+	+
Serum EPO	N/↓	N/↓	↓	↓	↓	↓	variable
Erythrocytes × 10^{12}/l	>5.8	<5.8	>5.8	>5.8	Around 5.8	Normal <5.5	Decreased
Leukocytes × 10^{9}/l	<12	Below 12	Above 12	< or >15	>20	N or ↑	>20
Platelets × 10^{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 (%) Grading reticulin fibrosis: RF Grading	50-80 RF 0-1 MF 0	50-80 RF 0-1 MF 0	60-100 RF 0-1 MF 0	80-100 RF 0/1 MF 0	80-100 RCF 1-3 MF 0/1	60-100 RCF 1-3 MF 0/2	Decreased RCF 3/4 MF 2/3

myelofibrosis: MF							
Splenomegaly grading							
Spleen size, echogram cm Spleen size on palpation cm	<12-15 0-3	<13 NP	12-15 0-3	12-16 4-6	18->20 >6	16>20 >6	>20 >8
JAK2^{V617F} in Granulocytes % JAK2^{V617F} in BFU-e (exon 12)	Low +(++)	Low +(++)	Moderate <50 +(++)	High>50 ++	High>50 ++	Mod/High +	High >50++
Risk stratification 2014 → Therapeutic implications	Low risk	Low risk	Low risk	Intermediate risk PV	High risk PV early MF	High risk PV In apparent PV	Post-PV MF Spent PV
First line Aspirin/Phlebotomy Second line IFN versus Hydroxyurea (HU) Third line JAK2 inhibitor	Aspirin Phlebotomy	Aspirin Phlebotomy	Phlebotomy Aspirin Low dose IFN → responsive	Phlebotomy* Aspirin IFN → resistant → HU	If IFN resistant → HU or JAK2 inhibitor	JAK2 Inhibitor First line	JAK2 Inhibitor → Bone marrow transplant

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

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