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MPD VOICE

Voice of the Myeloproliferative Disorders Community

FATIGUE & QUALITY OF LIFE

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INSIDE:

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From the President

Joyce Niblack

During the 2005 Mayo/CMPD Education Foundation conference, Dr. Ruben Mesa (Mayo Rochester) approached me with his idea for conducting a survey designed to determine what impact the myeloproliferative disorders have on the patient's quality of life. We've talked about the various constitutional symptoms that go along with these disorders on mpd-net and which are often brushed off by doctors. Well fortunately, Dr. Mesa "gets it". He, as Dr. Camoriano in particular, listen to their patients and are in tune with the fact that more than our counts are in issue. Dr. Mesa's goal was to identify and quantify what impact our MPDs have on quality of life issues and then work toward improving things for us. With that in mind, Dr. Mesa assembled a team of doctors from Mayo, MD Anderson and Dana Farber for this project and once the survey had Institutional Review Board approval, it was put up on a special web site and announced on mpd-net. 1179 Patients from 30 countries and 6 continents participated and the findings of this important study were published in ASH Abstracts and as an article titled The Burden of Fatigue and Quality of Life in Myeloproliferative Disorders, Cancer, Published online 22 November 2006. The co-authors are Ruben Mesa, MD, Mayo Rochester, Joyce Niblack, JD, CMPD Education Foundation, Martha Wadleigh, MD, Dana Farber, Srdan Verstovsek, MD, MD Anderson, John Camoriano, MD, Mayo Scottsdale, Sunni Barnes, PhD, Angelina Tan, MS, Pamela Atherton, MD, Jeff Sloan, PhD (all of Dana Farber), Ayalew Tefferi, MD, Mayo Rochester.

My deep personal thanks go to all who participated in this survey and to the doctors/researchers who devoted their time and efforts into finding how our lives are impacted by our diseases and are working to improve things for us.

Dr. Mesa will be addressing these findings and giving us his thoughts on ways to improve our quality of life at the February 23-25 2007 MPD Conference at Mayo Scottsdale. Those of you who are/were unable to attend can order the Conference DVD. Use the link on the home page of www.mpdinfo.org and complete the registration form, just checking off the DVD order ($80). The full Cancer article is included in the conference syllabus. No effort has been made in this newletter to discuss the details of methodology in designing the survey and analyzing the data. That is available in the actual journal article.

This newsletter summarizes the highlights of the findings of the QOL (Quality of Life Survey)

For those interested, reprints of the Mesa et al. Cancer article may be ordered by contacting **JNiblack@aol.com** or **LarryMilnes@comcast.net** after March 1.

The next issue of MPD VOICE will report the highlights of the February 23-25, 2007 Mayo/CMPD Education Foundation Patient-Doctor Conference.

1. Mayo Clinic, Scottsdale, Arizona
2. Fred Hutchinson Cancer Research Center, Seattle, Washington
3. Harvard Institutes of Medicine, Boston, Massachusetts
4. Mayo Clinic, Rochester, Minnesota
5. Mayo Clinic, Rochester, Minnesota
6. MD Anderson Cancer Center, Houston, Texas

THE BURDEN OF FATIGUE AND QUALITY OF LIFE IN MYELOPROLIFERATIVE DISORDERS (MPDs)

Ruben A. Mesa, MD, Mayo Rochester
Joyce R. Niblack, CMPD Education Foundation
John K. Camoriano, Mayo Scottdale

Summary

There have been frequent discussions on mpd-net about various constitutional symptoms that accompany myeloproliferative disorders. These include night sweats, pruritus, bone pain, fever, weight loss and fatigue. Until now, few objective data exist on the burden of fatigue and other constitutional symptoms in patients with myeloproliferative disorders. Hopefully, the survey using validated instruments of fatigue and physical assessment during an Internet-based symptom survey of 1179 MPD patients will provide a useful tool in working toward improving quality of life.

Summarizing the self-reported symptoms:

Fatigue	80.7%
Pruritis	52.2%
Night sweats	49.2%
Bone pain	13.7%
Weight loss	13.1%

In the majority of patients, these symptoms restricted participation in both social functions and physical activity. In addition, 34.5% of patients needed assistance with activities of daily living, and 11.2% reported MPD-associated medical disability. As expected, the presence of myelofibrosis, anemia, splenomegaly, or other features associated with advanced disease favored a higher degree of fatigue. However, fatigue remained the major complaint in polycythemia vera (84.9%) and essential thrombocythemia (72.4%). These figures were significanly higher than those of published controls ($P<0.0001$)

The investigators concluded that the current study identifies fatigue as the major contributor to poor quality of life in MPD patients, provides baseline information on constitutional symptoms and underscores the need for the incorporation of quality of life assessment in clinical trials.

Introduction

The BCR-ABL-negative, classic myeloproliferative disorders (MPDs) which include polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF) with myeloid metaplasia (MMM) have a cumulative incidence of approximately 6/100,000 each year and a median age at diagnosis of approximately 60 years. All MPDs can lead to premature death. In addition, quality of life (QOL) is adversely affected by a spectrum of disease complications including thrombosis, hemorrhage, microvascular symptoms, pruritus, spleen and liver enlargement, anemia, cachexia, and severe constitutional symptoms including fatigue and weight loss. Management of patients with ET and PV has focused on prophylaxis against thrombohemorrhagic complications by control of overproduction of red cells through therapeutic phlebotomy alone or with myelosuppression, overproduction of platelets through the use of platelet-lowering agents and antiplatelet therapy with aspirin. Unfortunately, current drug therapy is inadequate for patients with MMM in terms of both prolonging life and alleviation of symptoms, although allogeneic hematopoietic stem cell transplantation (HSCT) may benefit a selected group for young patients with poor prognostic factors and drugs such as Thalomid and Revlimid may improve anemia and other features in a subset of patients. Work continues for improved therapies for all MPD patients.

In addition to the objectively measured impact on marrow function, MPDs are associated with hypercatabolic symptoms that are best appreciated in the presence of weight loss and fever. What is not underscored however, is fatigue that is often present even in the absence of anemia and/or other advanced disease features and despite documentation of treatment-associated benefits in terms of blood counts and organomegaly. Furthermore, fatigue is a known and well-described side effect of the cytoreductive therapy used in MPDs: hydroxyurea, anagrelide and interferon-alpha. In the QOL survey, investigators used validated instruments to quantify the burden of fatigue and other disease-associated symptoms in MPD and to estimate their impact on QOL including physical activity and daily living.

Patients and Accrual

After approval from the involved institutions' institutional review boards, the survey was posted to the Internet to begin accrual of data. The survey did not contain any specific patient identifying information to avoid a conflict of HIPAA regulations (Health Insurance Portability and Accountability Act of 1996) and to avoid the requirement for written informed consent. Patients were recruited by either 1) informational sheets on the survey that contained the internet address

with which to access the survey or 2) a posting of the survey and background information to the mpd-net international online support group (mpd-net@listserv.acor.org) and on the **www.mpdinfo.org** website maintained by the patient advocate, Joyce Niblack. The websites are actively maintained as a source of communication for MPD patients and are in cooperation with the CMPD Education Foundation. Patients were welcomed to participate based on an established diagnosis of one of the three classic Philadelphia chromosome negative myeloproliferative disorders, polycythemia vera, essential thrombocythemia and agnogenic myeloid metaplasia. Given that the survey was available on the Internet in English with an approved Japanese translation, patients were welcomed to participate in a global fashion.

Survey Content

The survey collected patient demographics, employment status, MPD-specific information (diagnosis, treatment and complications), comorbidities (through the Charlson Co-Morbidity Index), results of 2 validated instruments that assessed fatigue and results of a physical activity assessment. In addition, the most recent sets of complete blood counts were requested (data was corrected for entry error for units, i.e. a leukocyte count of 3.4x109/L versus 3400)

Instrument description and scoring is available in detail in Cancer 22 November 2006 online.

Briefly:

Brief Fatigue Inventory (BFI) This 9-question survey allows the rating of specific fatigue items from 0-10 where 0=No Fatigue or does not interfere with activity and 10=As bad as you can imagine or completely interferes with activity

Functional Assessment of Cancer Therapy-Anemia (FACT-an) The FACT-an consists of 20 questions specific to symptoms associated with cancer-related anemia that are rated on a scale from 0-4 where 0=not at all and 4=very much. The Fact-an contains a fatigue-specific subscale comprised of 13 questions. Both the complete assessment and the subscale are scored by calculating the sum of all questions and converting the results into a 0-100 scale where 0 indicates poor QOL of life and 100 indicates high QOL.

Godin Leisure Time Activity Score (LAS) This assessment is a brief 4-item scale that assesses perceived barriers to physical activity where intensity and frequency of physical activity is recorded. During a 7 day period, subjects are asked to estimate the number of strenuous, moderate and mild exercises that lasted >15 minutes. The frequency of each intensity level is multiplied by the respective estimated energy expenditure in metaboloic equivalents (METs) for the activities (9 for strenuous, 5 for moderate, 3 for mild) to obtain physical activity scores.

Survey Administration The survey was available on the Internet (**http://survey.venturecs.net/myeolpro.htm**) for accrual and response from June 15 through December 15, 2005. Patients were asked to complete the survey only once and to provide answers as completely and accurately as possible. There was no external conformation of the responses provided. All results were immediately downloaded to a central computer server administered by the Mayo Survey Research Center.

Statistical Analysis Demographic and MPD-specific information were compiled, and descriptive statistics were computed for describing the patient population. Results from the Charlson Co-Morbidity Index, BFI, Fact-An, and LAS were scored according to the appropriate algorithm. Summary statistics were compiled for all patients. Further comparison of means for the Fact-An, Fact-An fatigue subscale, and BFI scores were preformed between MPD diagnosis and by other patient characteristics such as therapy, symptoms and hematologic counts. Our patient population mean scores for the BFI and Fact-An were copared with published norms. Spearman correlation coefficients were calculated to discern a relation between MPD characterization and QOL results. Furthermore, multifactorial analysis was conducted using regression ANOVA procedures and Fact-an scores to identify any predictive qualities of patient characteristics.

RESULTS

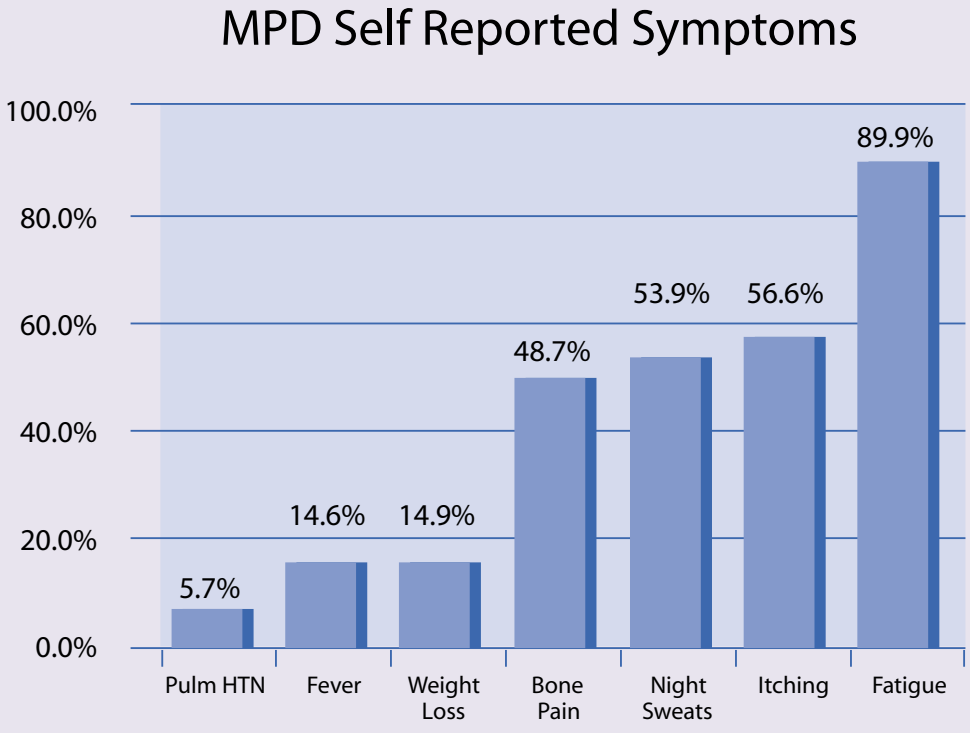
There were 1179 MPD patients who responded to the Internet-based survey over the study interval. These individuals were from a broad geographic distribution with 898 residing in the United States. The balance of patients (281) resided in 6 continents and 30 separate countries. Patients were of a varied age (median 56 years old); range 12-99; although the median is expected, the extreme range in age may reflect a respondent entry error). Respondents had been diagnosed a median of 5 years (range 0-56) before completing the survey, and reflected a sex distribution (men 41.4%) that was consistent with past Internet-based research with MPDs. Respondents represented a balanced range of MPD diagnoses including PV (405) 34.8%, ET(304) 26.1% and MMM (456) 39.1%. Among those patients with MMM, the subsets of their diseases were most accurately categorized as agnogenic myeloid metaplasia (AMM)(71.6%), post thrombocythemic myeloid metaplasia (PTMMM) (13.9%) or post polycythemic myeloid metaplasia (PPMM)(14.4%), respectively).

A history of thrombosis (n=261, 21.1%) and/or hemorrhage (n-272; 23.1%) was reported in approximately a quarter of patients. In addition (42.8% (n-478) of respondents reported spleen enlargement with 21% (n=231) reporting at least occasional pain or discomfort from the enlarged spleen. Anemia occurred in 39% of patients with 10.1% of these having hemoglobin <10 g/dL). Seven percent of patients were dependent on erythrocyte transfusion. Leukopenia (leukocyte count <3.5%x109 /L) occurred in 7%. Thrombocytopenia (platelet count <100 x 109/L) occurred in 10.6%, 4.6% of which had platelet counts below 50. Conversely, many patients still maintained evidence of very active myeloproliferation (based on most recently submitted blood counts) featuring uncontrolled erythrocytosis (hematocrit >45 in men, >42 in women; 5.2% leukocytosis (leukocytes <10.5) or thrombocytosis (platelets <450 x109/L, whereas 2.2% had platelets greater than 1 million.

The vast majority of respondents had undergone at least 1 form of therapy including phlebotomy (44.1%), splenectomy (3.7%), allogeneic stem cell transplant (1.2%) and some form of medical therapy (70.5%). Prior medical therapies included aspirin (63.6%), hydroxyurea (54.5%), anagrelide (34.1%), interferon-alpha (17%), corticosteroids (6.3%), thalidomide (4.6%), busulfan (2.4%), androgens (2%) and radioactive phosphorus (1.2%). There were 8.8% of patients who received some other form of MPD therapy.

THE MAJORITY OF MPD RESPONDENTS DESCRIBED SIGNIFICANT SYMPTOMS AND MEDICAL DISABILITY SECONDARY TO THEIR MPD

Characterization of subjective symptoms described by respondents demonstrated that MPD patients suffer from significant fatigue with 80.7% (n=952) self-reporting fatigue. Additional symptoms included pruritus (52.5%), night sweats (49.2%), fevers (13.7%) and undesired weight loss (13.1%). Further symptomatic breakdown by specific MPD diagnosis is provided in Table 2. MPDs also have a significant affect on patients' ability to work. Although the majority (52.1%) of patients work outside the home, 14.2% reported being medically disabled. The majority of this latter group, 11.2% of all respondents, were disabled specifically because of their MPD. In addition, 25.3% are currently retired.



Mesa et. al. Cancer 2007;109:68-76

MPD PATENTS SUFFER FROM SIGNIFICANT FATIGUE COMPARED WITH PUBLISHED NORMS

Fatigue (self-described as related to their underlying MPD diagnosis in 78.7% (n=928) quantification through the BFI and FACT-AN demonstrated that MPD patients have increased fatigue compared with published norms. Fatigue scores differed between MPD diagnosis where, although increased burden of fatigue was present across all MPD diagnoses, it was more pronounced in MMM patients. Within the group of patients with MPD type MMM, the subtype of disease (agnogenic myeloid metaplasia vs postpolycythemic versus post-thrombocythemic myeloid metaplasia) did not have an impact on the burden of fatigue

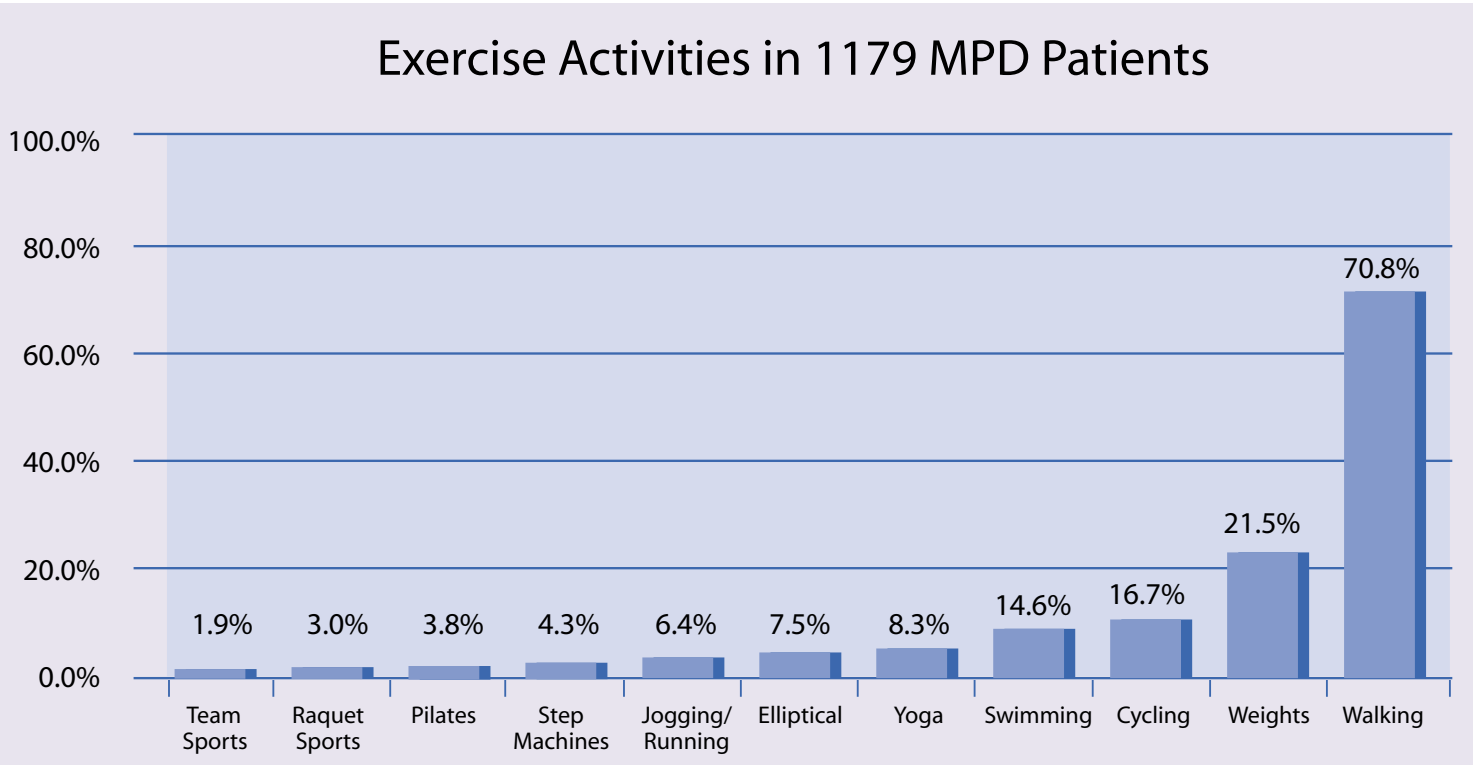
Disease-Related Features

Fatigue is frequently a multi-factorial process whether in MPD patients or the general population. As anticipated, the degree of fatigue described by respondents correlated with advanced disease features, types of MPD therapy, and known complications of their underlying disease. Not unexpectedly, fatigue is more common in patients with myelofibrosis. PTMM and PVMM patients had more significant fatigue than their ET and PV counterparts, respectively. In addition, and not unexpectedly, the presence of anemia led to a stepwise increase in fatigue from mild anemia (just below normal), to significant anemia (hemoglobin < 10 g/dL), to erythrocyte transfusion dependence. In addition, the presence of other symptoms (ie, pruritus, fever, weight loss) or prior MPD-related thrombohemorrhagic complications were all associated with increasing fatigue. Patients who currently smoke are also clearly more fatigued than their nonsmoking counterparts.

Fatigue is a problem even in the majority of patients with early stages of MPDs (asymptomatic). The survey included a group (n-279, 23.6%) of patients (PV 41.5%, ET 31%, MMM 24.7%) who denied any features typically thought to be signs of problematic MPD. Specifically, these are a history of thrombohemorrhagic events, splenomegaly, or anemia. These individuals reported fatigue measured by the FACT-An scores were significantly greater than published norms. In addition, when BFI was used, these values for the FACT-An appeared similar or worse than in patients who received chemotherapy for hematologic malignancies and were equivalent to non-Hodgkin lymphoma patients (and only slightly better than those with overt acute leukemia.

MPD-Related Fatigue May Be Exacerbated by Lack of Sufficient Activity

The impact of an MPD and the associated complications and symptoms can lead to a decrease in appropriate levels of physical activity for a variety of reasons. Indeed, we hypothesized that the fatigue from MPDs leads to further inactivity, which adds to a vicious cycle of inactivity, loss of lean muscle mass, and hence more fatigue. Respondents reported less physical activity than published controls on the LAS. MPD patients had 25.2 metabolic equivalents (METS) compared with 45.8 METS for controls.



MPD-Related Fatigue Correlates with Many Disease-Related Features

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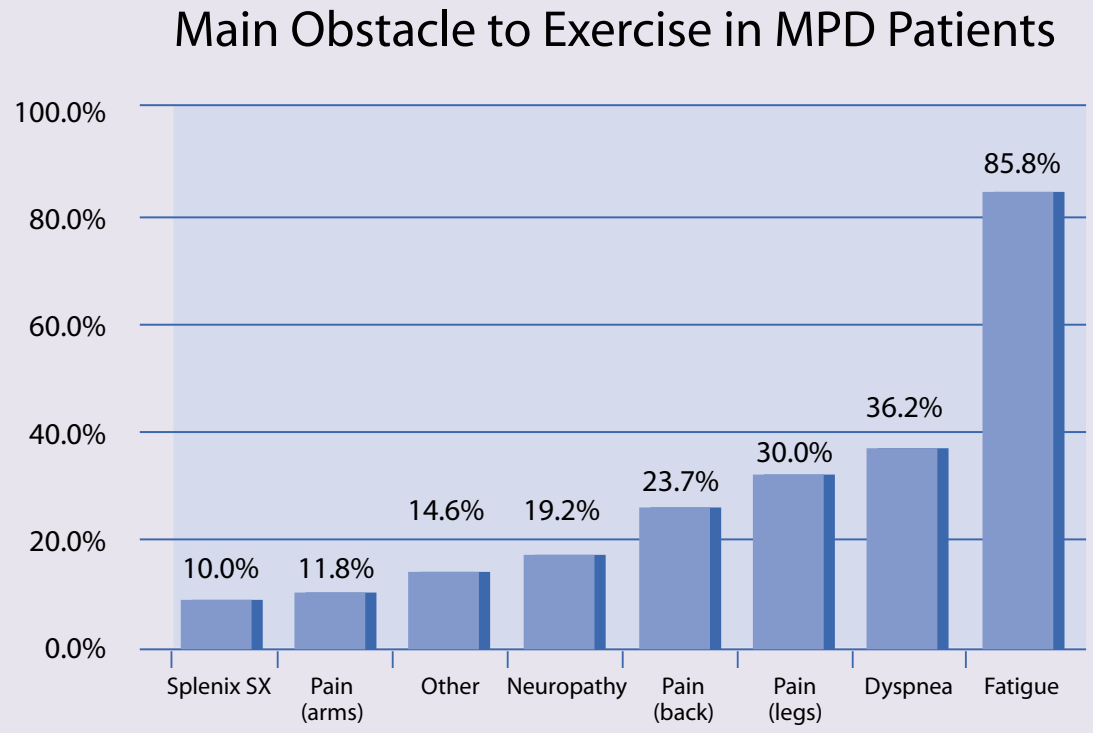

CONCLUSION

Patients with MPDs have long been know to suffer from a series of objective problems related to their hematologic disorder. Specifically, it has been demonstrated that MPD patients are at risk for thrombotic events in both small and large venous and arterial vessels. In addition, as patients have progressive or advanced disease (MMM de novo or secondary to ET or PV), they experience progressive drop in blood counts (cytopenias), progressive spleen and/or liver enlargement and portal hypertension. MPD patients all have a risk of eventual transformation to acute leukemia and risk of premature death. In concert with these objective disease features, MPD patients have been noted to suffer from a range of "constitutional symptoms" but the burden and character of these symptoms have not been quantified well in the literature. The investigators demonstrated by using an international, geographically diverse group of

MPD patients that the majority of MPD patients suffer from the significant symptoms of fatigue, pruritus, night sweats and bone pain.

Fatigue, although long recognized as occurring in MPD patients, has been poorly quantified in the past because of the subjective nature of the complaint. By using 2 different instruments, the investigators from Mayo Clinic, Harvard and MD Anderson clearly demonstrated that all subsets of MPD patients suffer from significant fatigue compared with the published norms. The interesting aspect of this observation is that the fatigue is present across the spectrum of severity of disease, and it was not attributable to comorbidity or age. In addition, although fatigue was associated with features clearly contributory to fatigue (such as anemia), the vast majority of even "asymptomatic" MPD patients still have clearly definable fatigue that they attribute to their disease. The presence of this latter finding suggests that there is an aspect to the underlying myeloproliferative process that may well directly cause fatigue even in the absence of a clear source.

The National Comprehensive Cancer Network (NCCN) defines fatigue as a persistent, subjective sense of tiredness related to cancer or cancer therapy that interferes with usual functioning. Among cancer patients, fatigue is felt to be related to multiple contributory factors including anemia, therapeutic toxicity, tumor burden, tumor-related cachexia and a variety of contributory cytokines. Similarly, MPD patients share these later potential mechanisms of fatigue with cancer patients and manifest MPD-related hypermetabolism. Various key cytokines have been implicated in exacerbating fatigue in cancer patients, such as tumor necrosis factor alpha (TNF-_), interleukin-1 and interleukin-6). Recent reports demonstrate that fatigue in cancer patients correlates with alteration of function in proinflammatory cytokines, and that the degree of alteration may explain the broad variability seen in cancer-related fatigue not easily explainable by stage of disease.

The vast majority of patients who responded to the survey had significant fatigue despite therapy. How do we begin to target fatigue and QOL as therapeutic endpoints in MPDs? Fatigue, as a morbidity from a host of malignant disorders is common, yet pharmacologic stimulates to overcome/improve this symptom have rarely been successful. Exercise has the ability to potentially improve fatigue in patients with malignancies, but published data remains limited in scope. In a recent analysis of 26 published trials (mainly breast cancer patients and survivors) of exercise interventions in patients with malignancies, it was shown that 1) patients with compromised performance status from disease (and therapy) are able to undergo cardiovascular exercise safely and 2) with positive benefits reported including increased lean muscle mass, decreased fatigue, decreased resting heart rate and decreased stress.. Our 68 year old patient advocate, Joyce, whose PV is complicated by pulmonary hypertension and right heart failure, has seen her resting heart rate drop from over 100 to high 60's and her energy, strength and balance has greatly improved since starting cardio rehab (aerobic exercise, stretching with and without bands and light weights). Among patients with hematologic malignancies (data limited to patients who are either undergoing systemic chemotherapy or allogeneic stem cell transplantation) results were similarly encouraging.

MPD patients suffer from a significant burden of fatigue and constitutional symptoms that are both morbid and frequently in excess of what may be expected solely on overt disease manifestations. The lack of efficacy of currently available therapeutic options for these patients to abrogate fatigue is striking, and this must be considered in prescribing palliative therapy for these patients. When novel pharmacologic therapies are evaluated in these patients, improvements in fatigue and other constitutional symptoms should be rigorously assessed and considered in judging these agents. In addition, non-pharmacologic interventions (such as exercise) should be considered as alternative strategies for alleviating MPD associated fatigue.

Membership Application

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❑ Agnogenic Myeloid Metaplasia (AMM aka MF, IMF, MMM) ❑ Essential thrombocythemia (ET)

❑ Polycythemia Vera (PV) ❑ MF Secondary to ET or PV ❑ Chronic Myelogenous Leukemia (CML)

❑ Mastocytosis ❑ Eosinophilic Syndrome/leukemia

❑ Chronic monomyelocytic leukemia (CMML) ❑ Myelodysplastic Syndrome (MDS)

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