The Burden of Fatigue and Quality of Life in Myeloproliferative Disorders (MPDs)

An International Internet-Based Survey of 1179 MPD Patients

Ruben A. Mesa, MD[1]
Joyce Niblack, JD[2]
Martha Wadleigh, MD[3]
Srdan Verstovsek, MD[4]
John Camoriano, MD[5]
Sunni Barnes, PhD[6]
Angelina D. Tan, MS[6]
Pamela J. Atherton, MS[6]
Jeff A. Sloan, PhD[6]
Ayalew Tefferi, MD[1]

[1] Department of Hematology, Mayo Clinic, Rochester, Minnesota.

[2] Chronic Myeloproliferative Disorders Education Foundation, Scottsdale, Arizona.

[3] Department of Oncology, Dana Farber Cancer Institute, Boston, Massachusetts.

[4] Department of Hematology, University of Texas MD Anderson Cancer Center, Houston, Texas.

[5] Department of Hematology/Oncology, Mayo Clinic Scottsdale, Scottsdale, Arizona.

[6] Department of Cancer Center Statistics, Mayo Clinic Statistics, Rochester, Minnesota.

Supported in part by K23 CA96780 (R.A.M.) and the Myeloproliferative Disorders Foundation (R.A.M. and A.T.).

The authors of this article contributed as follows: Ruben A. Mesa, MD (designed trial, wrote manuscript); Joyce Niblack, JD (designed trial, wrote manuscript); Martha Wadleigh, MD (designed trial, reviewed/revised manuscript); Srdan Verstovsek, MD (designed trial, reviewed/revised manuscript); John Camoriano, MD (designed trial, reviewed/revised manuscript); Sunni Barnes, PhD (statistical design, administration of survey); Angelina D. Tan (statistical analysis, wrote manuscript); Pamela J. Atherton (statistical analysis, wrote manuscript); Jeff A. Sloan, PhD (statistical analysis, wrote manuscript); Ayalew Tefferi, MD (designed trial, wrote manuscript).

BACKGROUND. Few objective data exist on the burden of fatigue and other constitutional symptoms in patients with myeloproliferative disorders (MPD).

METHODS. The authors used validated instruments of fatigue and physical activity assessment during an Internet-based symptom survey of 1179 MPD patients (median age, 56 years; 41.4% men).

RESULTS. The frequency of self-reporting was 80.7% for fatigue, which was substantially higher than that of pruritus (52.2%), night sweats (49.2%), bone pain (43.9%), fever (13.7%), and 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 also in polycythemia vera (84.9%) and essential thrombocythemia (72.4%); these figures were significantly higher than those of published controls ($P < .0001$).

CONCLUSIONS. The current study identifies fatigue as the major contributor to poor quality of life in MPD, provides baseline information on constitutional symptoms, and underscores the need for the incorporation of quality of life assessment in clinical trials. ***Cancer* 2007;109:68–76.** © *2006 American Cancer Society.*

KEYWORDS: myeloproliferative disorders, fatigue, quality of life, constitutional symptoms, polycythemia vera, myelofibrosis.

The *BCR-ABL*-negative, classic myeloproliferative disorders (MPDs),[1] 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.[2] All MPDs lead to premature death.[3,4] In addition, quality of life (QOL) is adversely affected by a spectrum of disease complications including thrombosis, hemorrhage, microvascular symptoms, pruritus, hepatosplenomegaly, 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 erythrocytosis through therapeutic phlebotomy,[5] thrombocytosis through the use of platelet-lowering agents,[6] and antiplatelet therapy

Address for reprints: Ruben A. Mesa, MD, Division of Hematology, Mayo Clinic, 200 First St., SW, Rochester, Minnesota 55905; Fax: (507) 266-4972; E-mail: mesa.ruben@mayo.edu

Received August 14, 2006; revision received September 27, 2006; accepted October 23, 2006.

DOI 10.1002/cncr.22365
Published online 22 November 2006 in Wiley InterScience (www.interscience.wiley.com).

with aspirin.[7] 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 of young patients with poor prognostic factors.[8,9]

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 often 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.[10] Furthermore, fatigue is a known and well-described side effect of the cytoreductive therapy used in MPDs: hydroxyurea,[11] anagrelide,[11] and interferon-alpha.[12] In the current study, we 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.

MATERIALS AND METHODS

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 was devoid of any specific patient identifying information to avoid a conflict with 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, which was provided by participating institutions to MPD patients at the time of consultation or 2) a posting of the survey and study background information to the mpd-net international online support group (MPD-net@listserv.acor.org) and on the MPDinfo.org website maintained by the patient advocate (J.N.). 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 1 of the 3 classic (Philadelphia chromosome negative) myeloproliferative disorders, specifically 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[13]), results of 2 validated instruments that assessed fatigue and results of a physical activity assessment. In addition, the most recent set of complete blood counts were requested (data was corrected for entry error for units, ie, a leukocyte count of 3.4×10^9/L versus 3400).

Instrument description and scoring

Brief Fatigue Inventory (BFI)[14]. 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.* The BFI score is the mean of all 9 questions.

Functional Assessment of Cancer Therapy–Anemia (FACT-An)[15]. The Fact-An consists of 20 questions specific to symptoms associated with cancer-related anemia that are on a rated 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 result into a 0–100 scale where 0 indicates poor QOL, and 100 indicates high QOL.

Godin Leisure Time Activity Score (LAS)[16]. 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 metabolic equivalents (METs) for the activities (9 for strenuous, 5 for moderate, 3 for mild) to obtain 3 physical activity scores.

Survey administration

The survey was available on the Internet (http://survey.venturecs.net/myelopro.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 confirmation 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,[13] BFI, Fact-An, and LAS were scored according to the appropriate algorithm. Summary statistics were compiled for all patients. Further comparisons of means for the Fact-An, Fact-An fatigue subscale, and BFI scores were performed 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 compared with published norms.[14,16,17] Spearman correlation coefficients were calculated to discern a relation between MPD characterization and QOL results. Furthermore, multifactorial analysis was conducted using regression ANOVA procedures on Fact-An scores to identify any predictive qualities of patient characteristics.

RESULTS

Respondents Encompassed Full Range of MPD Clinical Characteristics

There were 1179 MPD patients who responded to the Internet-based survey over the study interval (Table 1). These individuals were from a broad geographic distribution with 898 (76%) of patients residing in the United States. The balance of patients (n = 281; 24%) resided in 6 continents and 30 separate countries. Patients were of a varied age (median, 56.0 years; range, 12–99; although the median is expected, the extreme range may reflect respondent entry error), had been diagnosed a median of 5.0 years (range, 0–56 years) before completing the survey, and reflected a sex distribution (men, 41.4%) that was consistent with past Internet-based research with MPDs.[18] Respondents represented a balanced range of MPD diagnoses including PV (n = 405) 34.8%, ET (n = 304) 26.1%, and MMM (n = 456) 39.1%. Among those patients with MMM, the subsets of their diseases were most accurately categorized as agnogeric myeloid metaplasia (AMM) (71.6%), post thrombocythemic myeloid metaplasia (PTMM) (13.9%), or post polycythemic myeloid metaplasia (PPMM) (14.4%), respectively).

A history of thrombosis (n = 261; 22.1%), and/or hemorrhage (n = 272; 23.1%) was reported in approximately a quarter of patients. In addition, 42.8% (n = 478) of respondents reported splenomegaly with 21% (n = 231) reporting at least occasional pain or discomfort from the enlarged spleen. Anemia occurred in 39% of the patients, with 10.1% of these having hemoglobin <10 g/dL. Seven percent of patients were dependent on erythrocyte transfusion. Leukopenia (leukocyte count $<3.5 \times 10^9$/L) occurred in 7%, and thrombocytopenia (platelet count $<100 \times 10^9$/L) occurred in 10.6%, 4.6% of which had $<50 \times 10^9$/L. Conversely, many patients still maintained evidence of very active myeloproliferation (based on most recently submitted blood counts) featuring uncontrolled erythrocytosis (hematocrit >45 in men and >42 in women; 5.2%), leukocytosis (leukocytes $>10.5 \times 10^9$/L; 32.5%), or thrombocytosis (platelets$<450 \times 10^9$/L; 37.6%), whereas 2.2% had platelets $>1000 \times 10^9$/L.

The vast majority of respondents had undergone at least 1 form of therapy for controlling their MPD including phlebotomy (44.1%), splenectomy (3.7%), allogeneic stem cell transplant (1.2%), and some form of medical therapy (70.5%). Prior medical therapies reported 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 (P^{32}) (1.2%). There were 8.8% of patients who received some other form of MPD therapy.

Majority of MPD Respondents Described Significant Symptoms and Medical Disability Secondary to Their MPD

Characterization of subjective symptoms from respondents demonstrated that MPD patients suffer from significant fatigue, with 80.7% (n = 952) self-reporting fatigue. Additional symptomatology included pruritus (52.2%), night sweats (49.2%), bone pain (43.9%), 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 effect upon afflicted patients' ability to work. Although the majority of MPD patients work outside the home (n = 604; 52.1%), 14.2% (n = 163) report being medically disabled. The majority of this latter group (n = 130; 11.2% of all respondents) were disabled specifically because of their MPD. In addition, 25.3% (n = 293) are currently retired.

MPD Patients Suffer From Significant Fatigue Compared With Published Norms

Fatigue (self-described as related to their underlying MPD diagnosis in 78.7% of patients [n = 928]) quantification through the BFI and FACT-An demonstrated that MPD patients have increased fatigue compared with published norms[14,17] (Table 3). Specifically, MPD respondents had a mean score of 47.3 (range, 3.8–79.2) of a possible 100 on the Fact-An Fatigue subscale. This value demonstrates a level of fatigue far in excess of published norms (mean, 77.1; difference $P < .0001$).[17] These observations were further corroborated by the mean survey BFI score of 4.9 of a possible 10 (with a range of 1–10.0, where the higher score indicates higher fatigue). The mean for the general population is 2.2 (difference, $P < .0001$).[14] Fatigue score differed between MPD diagnosis where, although the increased burden of fatigue was present across all MPD

TABLE 1
Characteristics of 1179 Myeloproliferative Patients Whom Responded to an International Internet-based Survey of Fatigue and Disease Symptoms

Patient characteristics by MPD diagnosis	Missing (N = 14)	PV (N = 405)	ET (N = 304)	MF (N = 456)	Total (N = 1179)	*P*
Current age						<.0001
No.	7	400	301	445	1146	
Median	64.0	56.0	53.0	58.0	56.0	
Range	(48.0–73.0)	(12.0–85.0)	(16.0–82.0)	(16.0–99.0)	(12.0–99.0)	
Sex						<.0001
Women	6	51%	77%	53%	59%	
Men	5	49%	23%	47%	41%	
Missing	3	4	4	3	11	
Work outside the home						<.0001
Yes	2	57%	61%	43%	52%	
No: Retired	3	25%	20%	29%	25%	
No: Medically disabled because of MPD	1	9%	5%	18%	11%	
No: Medically disabled other cause	1	3%	4%	2%	3%	
No: Personal choice (non-medical)	1	6%	10%	8%	8%	
No: Unknown Reason	1	0.7%	0.3%	0.4%	0.5%	
Missing	7	4	2	6	12	
Years from initial MPD Dx						<.0001
No.	9	401	302	454	1157	
Median	9.0	4.0	5.0	6.0	5.0	
Range	(3.0–9.0)	(0.0–36.0)	(0.0–40.0)	(0.0–56.0)	(0.0–56.0)	
Subtype of MMM						.6717
1				712%	72%	
2				14%	14%	
3				15%	14%	
Hemoglobin (g/dL)						<.0001
No.	6	280	155	336	771	
Median	13.1	14.0	12.7	12.0	13.1	
Range	(7.8–15.9)	(6.4–19.0)	(4.4–17.0)	(5.0–18.0)	(4.4–19.0)	
Erythrocyte transfusion dependent	3	2%	3%	20%	9%	<.0001
Hemoglobin < normal	2	20%	40%	56%	39%	
Leukocytes ($\times 10^9$/L)						<.0001
No.	6	256	165	289	710	
Median	7.2	9.9	6.9	7.6	7.9	
Range	(1.0–9.9)	(0.0–71.0)	(0.0–23.6)	(0.3–126.6)	(0.0–126.6)	
Platelets ($\times 10^9$/L)						<.0001
No.	6	298	277	342	917	
Median	334.5	382.0	460.0	323.5	389.0	
Range	(105.0–796.0)	(0.0–1058.0)	(1.0–1719.0)	(1.0–1390.0)	(0.0–1719.0)	
Splenomegaly	1	42%	24%	56%	43%	<.0001
Splenectomy	1	1%	3%	6%	4%	0.0006
History of thrombosis	1	24%	22%	21%	23%	.5637
Other	1	9%	11%	9%	9%	.6887
Deep venous thrombosis	0	10%	5%	6%	8%	.0194
Stroke	0	6%	7%	5%	6%	.6890
Myocardial infarction	0	3%	4%	3%	3%	.887
Pulmonary Embolus	0	2%	2%	2%	2%	.9512
History of Hemorrhage	1	25%	26%	22%	24%	.3816
Therapy						
Allogeneic bone marrow/stem cell transplant	0	0.5%	0	3%	1%	.0013
Phlebotomy	4	87%	4%	33%	44%	<.0001
Medications	4	66%	83%	67%	71%	<.0001
Aspirin	3	72%	77%	49%	64%	<.0001
Hydroxyurea	3	53%	63%	51%	55%	.0062
Anagrelide	2	22%	60%	29%	34%	<.0001
Interferon	0	16%	14%	21%	17%	.0387
Other	1	7%	6%	12%	9%	.0074
Corticosteroids	1	3%	2%	12%	6%	<.0001
Thalidomide	0	0.2%	0.3%	12%	5%	<.0001

(*continued*)

TABLE 1
(*continued*)

Patient characteristics by MPD diagnosis	Missing (N = 14)	PV (N = 405)	ET (N = 304)	MF (N = 456)	Total (N = 1179)	*P*
Busulfan	0	1%	2%	4%	2%	.0059
Androgens	2	0.5%	0	4%	2%	<.0001
Charlson Co-Morbidity Index						.3541
0–2	12	86%	89%	86%	87%	
3–5	1	12%	10%	11%	11%	
6+	1	3%	1%	4%	3%	

PV indicates polycythemia vera; ET, essential thrombocythemia; MF, myelofibrosis.

TABLE 2
Myeloproliferative Associated Constitutional Symptoms by Diagnosis

Symptoms	Missing (N = 14)	PV (N = 405)	ET (N = 304)	MF (N = 456)	Total (N = 1179)	*P*
Fatigue	7	85%	72%	84%	81%	<.0001
Itching	3	65%	40%	50%	53%	<.0001
Night sweats	4	49%	41%	56%	50%	.0002
Bone pain	4	43%	41%	47%	44%	.2480
Fevers	2	13%	9%	18%	14%	.0013
Undesired weight loss	0	10%	7%	20%	13%	<.0001
Spleen pain	4	4%	9%	7%	6%	<.0001

PV indicates polycythemia vera; ET, essential thrombocythemia; MF, myelofibrosis.

diagnoses, it was more pronounced in MMM patients ($P < .001$; Table 3). All 3 MPD diagnoses fatigue burden were significantly different from published controls ($P < .0001$ for all). Within the group of patients with MPD type MMM, the subtype of disease (agnogenic versus postpolycthemic versus post-thrombocythemic myeloid metaplasia) did not have an impact upon the burden of fatigue.

MPD-related Fatigue Correlates With Many Disease-related Features

Fatigue is frequently a multifactorial process whether in MPD patients or the general population. As anticipated, the degree of fatigue described by respondents correlated with advanced disease features, type of MPD therapy, and known complications of their underlying disease. Not unexpectedly, fatigue is more common in patients with myelofibrosis. PTMM and PPMM 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 (all $P < .01$). 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.

Patients With Minimal "Objective" Manifestations of Their MPD Suffer From Mild to Severe Fatigue

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 (mean, 51.6; standard deviation [SD], 18.33) and BFI (mean, 4.2; SD, 2.4) scores which were significantly greater than published norms ($P < .001$ for both). In addition, when we used the BFI, these values for the FACT-An appeared similar or worse than in patients who received chemotherapy for hematologic malignancies[19] and were equivalent to non-Hodgkin lymphoma patients (and only slightly better than those with overt acute leukemia).[20] MPD patients also reported the full range of other subjective symptomatology exhibited by patients with more advanced disease features including pruritus (43.4%), bone pain (35.5%), night sweats (35.1%), unexplained fevers (6.1%), and undesired weight loss (3.2%). Finally, 2.6% of these same patients reported being medically dis-

TABLE 3
Myeloproliferative Patient Fatigue and Activity Data Compared With Published Norms

Disease	No.	BFI Mean (SD)	FACT-An Mean (SD)	Godin LAS	*P* Value compared with controls	
					BFI	FACT-An
Controls (BFI)	275	2.2 (1.80)	—	—	—	—
Controls (FACT-An)	1078	—	77.1 (19.9)	—	—	—
Controls (Godin LAS)	306	—	—	45.8	—	—
MPD Patients (All)	1158	4.9 (2.42)	47.3 (19.03)	25.2 (24.8)	<.0001	<.0001
Essential thrombocythemia	300	4.4 (2.28)	51.6 (17.64)	27.5 (22.7)	<.0001	<.0001
Polycythemia vera	397	5.1 (2.45)	46.5 (19.82)	25.9 (26.1)	<.0001	<.0001
Myelofibrosis with myeloid metaplasia	450	5.2 (2.42)	45.5 (18.79)	23.1 (24.8)	<.0001	<.0001
Agnogenic/chronic idiopathic	146	5.4 (2.49)	45.3 (19.53)	18.3 (20.81)	<.0001	<.0001
Postpolycythemic	173	4.9 (2.37)	46.7 (18.40)	23 (22.78)	<.0001	<.0001
Post-thrombocythemic	133	5.4 (2.42)	44.4 (18.60)	28.4 (29.9)	<.0001	<.0001

Brief Fatigue Inventory (BFI):[14] The 9 items in the BFI were all on a scale from 0–10 where 0 = No Fatigue/Does not interfere with activity and 10 = As bad as you can imagine/Completely interferes with activity. The BFI score is the mean of all 9 questions.

FACT-An:[17] The Fact-An questions are on a scale from 0–4 where 0 = not at all and 4 = very much. The Fatigue subscale consists of 13 questions, and it is scored by calculating the sum of all questions and converting the result into a 0–100 scale where 0 = poor QOL and 100 = is high QOL. The Anemia subscale consists of the 13 fatigue questions plus 7 anemia specific questions. The Anemia scores are calculated in the same manner.

Godin Leisure Time Activity Score (LAS): Physical activity was then assessed through the Godin Leisure Time Index,[16] with perceived barriers to physical activity also being recorded. This latter, brief, 4-item scale is a self-reporting of exercise activity in terms of intensity and frequency over a 7-day period. Specifically subjects are asked to estimate the frequency strenuous, moderate, and mild exercise (for periods of >15 minutes) over a 7-day period. The frequency of each intensity level is then multiplied by the respective estimated energy expenditure in metabolic equivalents (METs) for the activities (9 for strenuous, 5 for moderate, 3 for mild).

abled from their constitutional symptoms arising from their MPD, and 115 of 279 were no longer working. The majority (53%) of patients in this latter group were <65 years of age.

Fatigue Is a Major Problem in MPD Patients Despite Therapy and Normal Comorbidity Burden

In an attempt to quantify the possible contributing effect of comorbid conditions on the respondents the survey included the Charlson Co-Morbidity Index questionnaire.[13] This validated measure showed that the vast majority of individuals (86.8%) had 0–2 positive responses on the 10 point comorbidity score. These values are similar to age matched controls from the published literature[13] and supports our hypothesis that the increased fatigue burden is related to their underlying disease and not a manifestation of comorbidities due to age.

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 25.1 metabolic equivalents (METS) compared with 45.8 METS for controls.[16] The mean values for MPD patients were similar to mean scores published for patients with Parkinson disease (mean, 28.3).[21] The main barriers to partaking in appropriate levels of physical activity in the MPD patients were reported as fatigue (69.2%), dyspnea (30.8%), pain in legs (24.9%), pain in back (17.7%), numbness in legs and/or hands (15.6%), pain in arms (9.3%), and splenic pain and/or mass (8%). The majority (70.8%) of respondents felt that walking was an activity that could be pursued and was performed to some degree, but not as much as desired. Other common activities were weight training (21.5%), cycling (16.7%), and swimming (14%). All other forms of exercise were pursued by <10% of the patients (Fig. 1).

DISCUSSION

Patients with MPDs have long been known to suffer from a series of objective problems related to their hematologic disorder.[22] Specifically, it has been demonstrated that these patients are at risk of thrombotic events (both microvascular and macrovascular) in both venous and arterial sites.[23] In addition, as patients have progressive or advanced disease (namely MMM either de novo or secondary to a priori MPD) patients experience progressive cytopenias, progressive hepatosplenomegaly, and portal hypertension.[24] These patients all have a risk of eventual transforma-

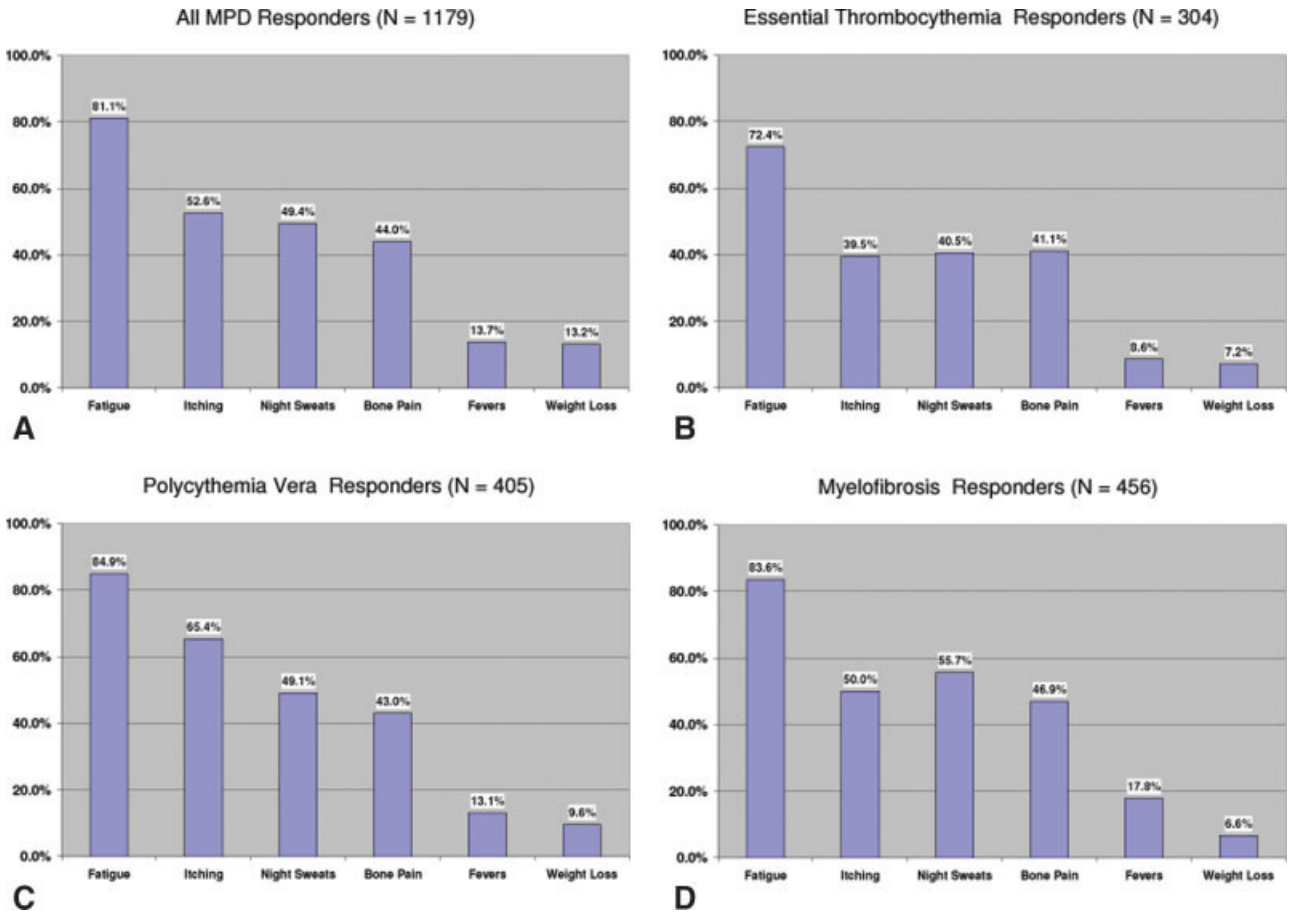

FIGURE 1. Myeloproliferative disorders self-reported symptoms in (A) all responders to the survey, (B) the subset with essential thrombocythemia, (C) polycythemia vera, and (D) myelofibrosis with myeloid metaplasia.

tion to acute leukemia and risk of premature death.[24] 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 been not been quantified well in the literature. We have 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.

The authors fully acknowledge the limitations inherent in patient self-reporting of clinical information. There were potential inaccurate entries of blood counts and the possibility that survey respondents incorrectly selected the wrong MPD. In addition, there is the potential for bias from the inclusion of patients who have the education and financial resources to access the Internet or the potential that patients who were more symptomatic might have been more inclined to participate in such a survey. We think that although limitations are at play, given the uniform nature of our results and the tremendous overlap in phenotypic manifestations between MPD subgroups, these features and uncertainties do not detract from observations made. Namely, the vast majority of a large cross section of MPD patients suffer from moderate to severe fatigue that is not easily explained by anemia or medication toxicity.

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 distinct instruments, we clearly demonstrated that all subsets of MPD patients suffer from significant fatigue compared with 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.[25] Similarly, MPD patients share these latter 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-α), interleukin-1, and interleukin-6.[25] Indeed, recent reports demonstrate that fatigue in cancer patients correlates with alteration of function in proinflammatory cytokines,[26] 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 stimulants to abrogate this symptom have rarely been successful. Exercise has the ability to potentially improve fatigue in patients with malignancies, but published data remain limited in scope. In a recent analysis of 26 published trials (mainly breast cancer patients and survivors)[27] 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) positive benefits reported included increased lean tissue mass,[28] decreased fatigue,[29] decreased resting heart rate, and decreased stress. Among patients with hematologic malignancies (data limited to patients who are either undergoing systemic chemotherapy or allogeneic stem cell transplantation[30]) 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 based 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, nonpharmacologic interventions (such as potentially exercise) should be considered as alternative strategies for alleviating MPD associated fatigue.

REFERENCES

1. Tefferi A, Lasho TL, Schwager SM, et al. The clinical phenotype of wild-type, heterozygous, and homozygous JAK2V617F in polycythemia vera. *Cancer*. 2006;106:631–635.
2. Mesa RA, Silverstein MN, Jacobsen SJ, Wollan PC, Tefferi A. Population-based incidence and survival figures in essential thrombocythemia and agnogenic myeloid metaplasia: an Olmsted County Study, 1976–1995. *Am J Hematol*. 1999;61:10–15.
3. Dingli D, Schwager SM, Mesa RA, Li CY, Tefferi A. Prognosis in transplant-eligible patients with agnogenic myeloid metaplasia: a simple CBC-based scoring system. *Cancer*. 2006; 106:623–630.
4. Wolanskyj AP, Schwager SM, McClure RF, Larson DR, Tefferi A. Essential thrombocythemia beyond the first decade: life expectancy, long-term complication rates, and prognostic factors. *Mayo Clin Proc*. 2006;81:159–166.
5. Berk PD, Goldberg JD, Donovan PB, Fruchtman SM, Berlin NI, Wasserman LR. Therapeutic recommendations in polycythemia vera based on Polycythemia Vera Study Group protocols. *Semin Hematol*. 1986;23:132–143.
6. Cortelazzo S, Finazzi G, Ruggeri M, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. *N Engl J Med*. 1995;332:1132–1136.
7. Landolfi R, Marchioli R, Kutti J, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. *N Engl J Med*. 2004; 350:114–124.
8. Mesa RA, Powell H, Lasho T, Dewald GW, McClure R, Tefferi A. A longitudinal study of the JAK2(V617F) mutation in myelofibrosis with myeloid metaplasia: analysis at two time points. *Haematologica*. 2006;91:415–416.
9. Deeg HJ, Gooley TA, Flowers ME, et al. Allogeneic hematopoietic stem cell transplantation for myelofibrosis. *Blood*. 2003;102:3912–3918.
10. Mesa RA, Steensma DP, Pardanani A, et al. A phase 2 trial of combination low-dose thalidomide and prednisone for the treatment of myelofibrosis with myeloid metaplasia. *Blood*. 2003;101:2534–2541.
11. Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med*. 2005;353:33–45.
12. Merup M, Aberg W, Lofvenberg E, et al. Symptoms, symptom distress and health-related quality of life in patients with polycythaemia vera or essential thrombocythaemia during treatment with interferon-alpha. *Acta Oncol*. 2002;41:50–55.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40: 373–383.
14. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer*. 1999;85:1186–1196.
15. Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. *Semin Hematol*. 1997;34(3 suppl 2):13–19.
16. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. *Can J Appl Sport Sci*. 1985;10: 141–146.

17. Cella D, Zagari MJ, Vandoros C, Gagnon DD, Hurtz H-J, Nortier JWR. Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. *J Clin Oncol*. 2003;21:366–373.
18. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell*. 2005;7:387–397.
19. Straus DJ, Testa MA, Sarokhan BJ, et al. Quality-of-life and health benefits of early treatment of mild anemia: a randomized trial of epoetin alfa in patients receiving chemotherapy for hematologic malignancies. *Cancer*. 2006;107:1909–1917.
20. Wang XS, Giralt SA, Mendoza TR, et al. Clinical factors associated with cancer-related fatigue in patients being treated for leukemia and non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20:1319–1328.
21. Garber CE, Friedman JH. Effects of fatigue on physical activity and function in patients with Parkinson's disease. *Neurology*. 2003;60:1119–1124.
22. Dameshek W. Some speculations on the myeloproliferative syndrome. *Blood*. 1951;6:372–375.
23. Elliott MA, Tefferi A. Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. *Br J Haematol*. 2005;128:275–290.
24. Tefferi A. Myelofibrosis with myeloid metaplasia. *N Engl J Med*. 2000;342:1255–1265.
25. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. *Lancet*. 2003;362:640–650.
26. Collado-Hidalgo A, Bower JE, Ganz PA, Cole SW, Irwin MR. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. *Clin Cancer Res*. 2006;12:2759–2766.
27. Galvao DA, Newton RU. Review of exercise intervention studies in cancer patients. *J Clin Oncol*. 2005;23:899–909.
28. Winningham ML, MacVicar MG, Bondoc M, Anderson JI, Minton JP. Effect of aerobic exercise on body weight and composition in patients with breast cancer on adjuvant chemotherapy. *Oncol Nurs Forum*. 1989;16:683–689.
29. Winningham ML, Nail LM, Burke MB, et al. Fatigue and the cancer experience: the state of the knowledge. *Oncol Nurs Forum*. 1994;21:23–36.
30. Hayes S, Davies PS, Parker T, Bashford J, Newman B. Quality of life changes following peripheral blood stem cell transplantation and participation in a mixed-type, moderate-intensity, exercise program. *Bone Marrow Transplant*. 2004;33:553–558.