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The Myelofibrosis Symptom Assessment Form (MFSAF): An Evidence-based Brief Inventory to Measure Quality of Life and Symptomatic Response to Treatment in Myelofibrosis

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Abstract

Quality of life (QoL) in patients with myelofibrosis (MF) is severely compromised by severe constitutional symptoms (i.e. fatigue, night sweats, fever, weight loss), pruritus, and symptoms from frequently massive hepatosplenomegaly. Given that no current instrument of patient reported outcomes (PRO) exists that covers the unique spectrum of symptomatology seen in MF patients, we sought to develop a new PRO instrument for MF patients for use in therapeutic clinical trials. Utilizing data from an international internet based survey of 458 patients with MF we created a 20 item instrument (MFSAF: Myelofibrosis Symptom Assessment Form) which measures the symptoms reported by >10% of MF patients, and includes a measure of QoL. We subsequently validated the MFSAF in a prospective trial of MF patients involving patient and provider feedback, as well as comparison to other validated instruments used in cancer patients. The

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RAM and AT wrote the paper and designed the quality of life and symptom assessment form (MFSAF). RAM is the principal investigator of the quality of life survey in myelofibrosis patients. All other authors reviewed the MFSAF, enrolled patients in the prospective portion of the trial and provided input and approved the final draft of the paper.

MFSAF results were highly correlated with other instruments, judged comprehensive and understandable by patients, and should be considered for evaluation of MF symptoms in therapeutic trials.

Keywords

Myelofibrosis; myeloproliferative disorder; primary myelofibrosis; fatigue; splenomegaly

Introduction

Myelofibrosis (MF), including primary (PMF), post polycythemia vera (post-PV MF), and post essential thrombocythemia (post-ET MF), not only shortens survival but also severely compromises quality of life (QoL) as a result of marked splenomegaly and profound constitutional symptoms that are believed to be cytokine-mediated: e.g. fatigue, night sweats, fever or uncomfortable feeling of warmth, weight loss, peripheral edema, pruritus, bone pain, dyspnea, and intractable cough[1]. In a recently published international internet based survey of 1179 patients, we used the Brief Fatigue Inventory (BFI), to demonstrate that patients with PV, ET, and PMF suffer from substantial fatigue that is in excess of what is expected from age-matched controls and not necessarily attributed to the presence of anemia[1]. The latter study also demonstrated that current drug therapy, which includes hydroxyurea, interferon, thalidomide, corticosteroids, androgen preparations, and erythropoiesis stimulating agents, is suboptimal in alleviating fatigue or other constitutional symptoms associated with the aforementioned myeloproliferative neoplasms (MPNs).

The recent discovery of $JAK2^{V617F}$ in close association with MPNs has led to the development of small molecule JAK2 inhibitors that have already been introduced into clinical trials in humans. Initial results of the small molecule JAK2 inhibitors suggest a profound effect, from such drugs, upon splenomegaly, constitutional symptoms and cachexia[2]. One challenge in the analysis, or comparison, of the aforementioned trials is that no current validated instrument exists for measurement of the spectrum of PRO for the presence or improvement of symptoms in MF patients. Therefore we used evidence from the above-mentioned internet-based QoL survey to create an MF-specific QoL and symptom assessment form (MFSAF: Myelofibrosis Symptom Assessment Form), and subsequently validated the form in a prospective manner.

Methods

Creating the MFSAF from MF QoL Data

Our main objective was to establish a new and evidence-based symptom and QoL assessment tool for MF. To that end, we started with information that was already available from a previously published internet based survey of symptoms involving patients with MF, PV, or ET[1]. We then performed a, previously unpublished, subset analysis that includes only MF patients stratified into PMF, post-PV MF, and post-ET MF (Table 1) for identifying the key symptoms from which these patients suffer, with special emphasis in the severe fatigue from which they are afflicted (Table 2). We built a 20 item MF specific PRO instrument

focusing upon the presence and severity of the symptoms primarily identified by MF patients in our survey.

MFSAF Content (Table 3)

Fatigue: Fatigue is a central complaint in MF (Table 1) therefore we chose to include in its entirety the previously validated brief fatigue instrument (BFI)[3] (that worked well in our MPN study (Table 2)) to quantitate fatigue.

Splenomegaly associated symptoms: The clinical impact of splenomegaly is measured by the patients perception of early satiety, abdominal pain (or discomfort), inactivity, and cough from diaphragmatic irritation all on a 0 (absent) to 10 (worst imaginable) scale.

Catabolic/Proliferative Symptoms: Next we quantify catabolic and proliferative symptoms specifically identified from the QOL study (night sweats, itching, bone pain, fever and weight loss) using a 0 (absent) to 10 (worst imaginable) scale

QOL: Overall QOL is measured in the validated 0 (as good as it can be) to 10 (as bad as it can be) scale.

Initial Validation of the MFSAF

Reaching validation of any instrument of patient symptoms is an ongoing process as opposed to a finite endpoint, this is particularly true with a heterogeneous disease such as MF. After IRB approval was obtained, we prospectively enrolled MPN patients in a validation study of the MFSAF study at the time of a clinical outpatient visit. After completing the MFSAF patients were asked to assess the instrument in terms of ease of understanding, and whether all of their MF associated symptoms were assessed. A free text box was also offered for describing symptoms not included in the form. Additionally, patients completed other symptom based instruments (previously validated elsewhere) which incorporated some of the MF associated symptoms addressed in the MFSAF, results between the instruments were correlated for agreement. Instruments utilized for this purpose included the Memorial Symptom Assessment Scale (MSAS)[4] and the Brief Pain Inventory (BPI)[5]. Physician input was included including their assessment of patient's fatigue, spleen symptoms, and quality of life (blinded to patient's responses) as well as clinical history, lab and exam findings.

Results

MFSAF Results (Table 4)

34 MPN patients were enrolled (24 MF, 10 in the comparison group (4 polycythemia vera (PV), 6 essential thrombocythemia (ET)). The MFSAF was rated by patients as easy to understand (median score 1, range 0–6), and "addressed most of my symptoms" (median score 1, range 0–6) both on a scale of 0 (as good as possible to 10 as bad as possible). When asked if a symptom was not addressed (open ended response) no single symptom was named more than once. As we have previously reported fatigue was common with BFI mean score of 4.0 (lower/upper 95% CI 2.8/5.2)) for MF and mean 2.4 (lower/upper 95% CI 1.7/3.1))

for the ET/PV group. Increasing BFI scores are associated with worsening fatigue with published "healthy" controls achieving a 2.2 (Table 2). Additional MF associated symptoms were captured well by the MFSAF with splenic, constitutional symptoms, and QOL documented easily and worse than ET/PV controls (Table 4). Physician's estimation of their patient's QoL corresponded very well (median 3 (0–8) for MF, median 2 (0–4) for ET/PV) (Table 4).

MFSAF Comparison to other Instruments

The MFSAF performed very well for assessment of specific symptoms addressed in the validated MSAS[4]. Specifically, corresponding questions from the MSAS were all highly correlated (all $p<0.01$) with MFSAF counterparts (in italic) including lack of energy *(fatigue)*, cough (*same*), pain (both *abdominal pain* and *bone pain*), sweats (*night sweats*), itching (*same*), and weight loss (*same*). Further validation of pain measurements in the MFSAF came from comparison to the BPI where both individually the presence, and intensity of pain (both abdominal and bone) were highly correlated (all $p<0.01$).

Discussion

We have created a simple, easy to understand, comprehensive 20 item instrument for capturing the critical and most prevalent symptoms arising in patients with myelofibrosis through the MFSAF. Although many instruments of PRO exist for cancer patients, none capture in an effective manner the spectrum of symptoms from pruritus, fatigue, and splenic symptoms seen in MF patients. The prospective validation of the MFSAF in MPN patients further demonstrates the ability of the instrument to capture the presence and intensity of the primary disease associated symptoms.

Symptomatic measurement in patients with MF is essential for 2 key reasons. The first is that the presence of constitutional symptoms has recently been reported by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) to be an adverse prognostic factor in estimating survival by the MF IPSS[6]. Second, a systematic way of measuring MF associated symptoms is critical for evaluating the impact of JAK2 inhibitors and other novel therapies on the symptomatic burden in these patients. We would strongly encourage our colleagues involved in administering therapeutic trials in MF patients to include a serial analysis on MF symptoms through the MFSAF so that symptomatic benefit (or detriment) of parallel therapeutic trials might be compared.

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Table 1

Self-Reported Constitutional Symptoms in 458 Patients with Myelofibrosis

Symptom	PMF (N=148; 32.3%)	Post PV MF (N=174; 38%)	Post ET MF (N=136; 29.7%)	All patients (N=458)	P value
Fatigue	*85%*	*81%*	*85%*	*84%*	*0.56*
Bone Pain	*51%*	*46%*	*44%*	*47%*	*0.51*
Fever	*19%*	*17%*	*18%*	*18%*	*0.87*
Pruritus	*39%*	***69%***	*39%*	*50%*	***<0.01***
Night Sweats	*55%*	*58%*	*53%*	*56%*	*0.67*
Symptomatic Splenomegaly	***76%***	*49%*	*41%*	*54%*	***<0.01***
Weight Loss (>10%)	***30%***	*15%*	*16%*	*20%*	***<0.01***

PMF (Primary Myelofibrosis)

Post PV MF (Post Polycythemia Vera Myelofibrosis)

Post ET MF (Post Essential Thrombocythemia Myelofibrosis)

Table 2

Comparison of Self Reported Fatigue in Patients with Myelofibrosis Compared to Published Norms

Disease	N	BFI Mean (SD)	P Value Compared to Controls
Myelofibrosis (Total)	**458**	**5.2 (2.42)**	P<0.001
• *Primary Myelofibrosis*	*148*	*5.4 (2.49)*	P<0.001
• *Post PV MF*	*174*	*4.9 (2.37)*	P<0.001
• *Post ET MF*	*136*	*5.4 (2.42)*	P<0.001
Controls (BFI)	275	2.2 (1.80)	-----
Controls (FACT-An)	1078	----	-----

Brief Fatigue Inventory (BFI)[3]: The nine 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 nine questions.

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Table 3

Myelofibrosis - Symptom Assessment Form (MF-SAF)

	Symptom	**1 to 10 (0 if absent) ranking* 1 is most favorable and 10 least favorable**			
Fatigue (Brief Fatigue Inventory)	Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW	0 (No Fatigue)		1 2 3 4 5 6 7 8 9	10 (Worst Imaginable)
	Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL Level of fatigue during past 24 hours	0 (No Fatigue)		1 2 3 4 5 6 7 8 9	10 (Worst Imaginable)
	Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	0 (No Fatigue)		1 2 3 4 5 6 7 8 9	10 (Worst Imaginable)
	Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your				
	• General Activity	0 (Does not Interfere)		1 2 3 4 5 6 7 8 9	10 (Completely Interferes)
	• Mood	0 (Does not Interfere)		1 2 3 4 5 6 7 8 9	10 (Completely Interferes)
	• Walking ability	0 (Does not Interfere)		1 2 3 4 5 6 7 8 9	10 (Completely Interferes)
	• Normal Work (includes work both outside the home and daily chores)	0 (Does not Interfere)		1 2 3 4 5 6 7 8 9	10 (Completely Interferes)
	• Relations with other people	0 (Does not Interfere)		1 2 3 4 5 6 7 8 9	10 (Completely Interferes)
	• Enjoyment of life	0 (Does not Interfere)		1 2 3 4 5 6 7 8 9	10 (Completely Interferes)
Splenomegaly and associated mechanical symptoms	Filling up quickly when you eat (Early Satiety)	Examples	0 (Absent) 1 2 3 *Does not limit how much you can eat*	4 5 6 7 *Moderately limits how much you can eat*	8 9 10 (Worst Imaginable), *Severely limits how much you can eat*
	Abdominal pain or discomfort	Examples	0 (Absent) 1 2 3 *Present but do not consider an issue*	4 5 6 7 *Definitely an issue but not requiring medications*	8 9 10 (Worst Imaginable), *Severe enough to require medications*
	Inactivity	Examples	0 (Absent) 1 2 3 *limited only with strenuous exercise*	4 5 6 7 *Even simple walking is a difficult task*	8 9 10 (Worst Imaginable), *Mostly chair or bed ridden*
	Cough	Examples	0 (Absent) 1 2 3 *Present but do not consider an issue*	4 5 6 7 *Definitely an issue but not requiring medications*	8 9 10 (Worst Imaginable), *Severe enough to require medications*
Other patient reported symptoms derived from	Night Sweats	Examples	0 (Absent) 1 2 3 *Noticeable but do not need to change garment or sheets*	4 5 6 7 *Garment change but able to sleep*	8 9 10 (Worst Imaginable), *Garment change and interferes with sleep*

	Symptom	**1 to 10 (0 if absent) ranking* 1 is most favorable and 10 least favorable**			
an international patient survey	Itching (pruritus)	Examples	0 (Absent) 1 2 3 *Present but do not consider an issue*	4 5 6 7 *Definitely an issue but not requiring medications*	8 9 10 (Worst Imaginable), *Severe enough to require medications*
	Bone Pain (diffuse not joint pain or arthritis)	Examples	0 (Absent) 1 2 3 *Present but do not consider an issue*	4 5 6 7 *Definitely an issue but not requiring medications*	8 9 10 (Worst Imaginable), *Severe enough to require medications*
	Documented fever at least once a week?	Yes or No If yes, state the actual temperature range: _____ C or F			
	Unintentional weight loss (i.e. not the result of planned weight loss such as diet +/− exercise) in the last 6 months in excess of 10 pounds?	Yes or No If yes, state how many pounds lost last 6 months:_____			
	What is your Overall Quality of Life?	0 (As good as it can be)		1 2 3 4 5 6 7 8 9	10 (As Bad as it can be)

Table 4

Results from the Myelofibrosis Symptom Assessment Form (MFSAF) in 34 patients with Myeloproliferative Neoplasms

	Myelofibrosis (N=24) ***(Mean; Upper 95%/Lower 95%)***	**Essential Thrombocythemia/Polycythemia Vera (N=10)** ***(Mean; Upper 95%/Lower 95%)***
Brief Fatigue Inventory Score [3]*A*	4.0 (2.8/5.2)	2.4 (1.7/3.1)
Early Satiety*B*	3.1 (2.0/4.2)	2.2 (0.2/4.2)
Abdominal Pain/Discomfort*B*	2.2 (1.0/3.4)	1 (0/2.0)
Inactivity*B*	2.7 (1.7/3.8)	1.2 (0.4/2.0)
Cough*B*	1.3 (0.4/2.1)	0.7 (0/1.6)
Night Sweats*B*	2.3 (1.0/3.6)	1.1 (0.2/2.0)
Itching*B*	1.9 (0.7/3.0)	1.4 (0/3.2)
Bone Pain*B*	2.0 (0.9/3.1)	1 (0/2.1)
Fever	Yes 17%	Yes 10%
Weight Loss	Yes 33%	Yes 10%
Overall Quality of Life*C*	3 (2.0/4.0)	1.5 (0.9/2.1)

A **Brief Fatigue Inventory (BFI)**[3]: The nine 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 nine questions.

B Self scored on a scale from 0 (Absent) to 10 (as bad as it can be)

C self scored on a scale from 0 (As good as it can be) to 10 (as bad as it can be)