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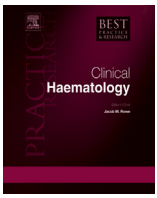

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Assessing disease burden in patients with classic MPNs

Holly Geyer, MD, Assistant Professor of Medicine [a],
Ruben A. Mesa, MD, Professor and Chair, Deputy Director [b, *]

[a] Division of Hospital Internal Medicine, Mayo Clinic, AZ, USA
[b] Division of Hematology and Medical Oncology, Mayo Clinic Cancer Center, Mayo Clinic, 13400 East Shea Boulevard, Scottsdale, AZ 85259, USA

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Myeloproliferative neoplasm (MPN) disorders including polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF), are recognized amongst the world of malignancies for their unique disease–burden profiles. Symptom management remains a prime directive for all MPN disorders. Limited by the dramatic heterogeneity and disparate severity amongst symptoms, only recently have researchers possessed the scoring tools necessary to quantify the MPN symptom burden and investigate its role in patient prognosis. In addition to symptom management, clinicians are also tasked with managing the numerous complications that arise from MPN progression including splenomegaly, cytopenias, thrombotic and hemorrhagic events and transformation to MF (from PV or ET) or acute myelogenous leukemia. In this article, we discuss the pleiotropic solidarity of the MPN symptom profile, inherent complications that define the disorders, available patient-reported outcome tools, the role of risk-scoring algorithms and open arenas for ongoing MPN symptom research.

Introduction

Introduced in their collective status by William Dameshek in 1951, myeloproliferative neoplasms (MPN's) are a distinctive grouping of stem cell hemopathies that result from the clonal dysregulation of

* Corresponding author.
E-mail addresses: hollygeyer@gmail.com (H. Geyer), mesa.ruben@mayo.edu (R.A. Mesa).

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myeloid precursors [1]. Polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) rank amongst the most frequently encountered MPNs and each is characterized by a unique symptom profile, course, response to treatment and prognosis. Polycythemia vera and essential thrombocythemia are typified by erythrocytosis and thrombocytosis, respectively, with a reduced symptom burden profile and limited impact on overall survival. In contradistinction, myelofibrosis, acknowledged, to be the most unfavorable MPN subtype, is discernable by marrow fibrosis, severe constitutional symptoms and impaired quality of life with a significantly reduced life expectancy of six to ten years [2]. Historical management of PV and ET has emphasized prophylaxis against thrombohemorrhagic complications with limited focus on symptom management given the paucity of available therapeutic agents. In contrast, management of MF has been largely symptom based with stem cell transplant being the only curative option.

Assessment of the MPN disease burden requires addressing both patient symptomatology and disease complications. Patient symptomatology may be exceptionally burdensome and in itself contribute to premature mortality. The requirement for precise assessment of the MPN symptom burden became evident with the 2005 discovery of the JAK2V617F mutation noted in PV (96%), PMF (65%) and ET (55%) [3–5]. Since then, a plethora of gene-targeted therapies including JAK2 inhibitors, MTOR inhibitors, HDAC inhibitors and immunomodulatory agents have emerged with the potential to impact both morbidity and mortality. As these therapies entered clinical trials, antiquated oncologic symptom assessment tools were quickly observed to lack the responsiveness necessary for objective quantification the MPN symptom burden and successive evaluation of therapy effectiveness. Development of the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) and its companion surveys (MF-SAF, MPN-SAF TSS) elegantly revealed the heterogeneity and severity of the MPN symptom burden while appraising the prospective roles for targeted therapy earlier in the disease process. Similarly, disease complications are a part of the natural history in MPN progression and may include life-threatening cytopenias, massive splenomegaly, thrombosis, bleeding complications and transformation to either MF (from PV or ET) or acute myelogenous leukemia (AML). Below we discuss the distinctiveness of the MPN disease–burden profile along with the resources and approach necessary for disease assessment.

Components of the MPN symptomatic burden

The MPN disease burden is heterogenous with an expansive spectrum of disease-related complaints. Though distinct symptoms may be observed more frequently than others within each MPN subtype, individual patient profiles are highly variable. Self-reporting of symptoms by MPN patients has identified fatigue (80.7%), pruritus (52.2%), night sweats (49.2%), bone pain (43.9%), fevers (13.7%) and undesired weight loss (13.1%) to be the most prevalent symptoms [2]. Management of MPN symptoms has been difficult given the objectionable side-effects inherent to available treatments [2]. With the majority of MPN patients describing impairment in overall quality of life (ET, 76.8%; PV, 85.5%; MF, 94.7%) [6] and 14.2% of MPN patients reporting medical disability, assessment of individual MPN symptoms has emerged as a research priority. Below, we briefly discuss the most prevalent and burdensome MPN symptoms (Table 1).

Fatigue

Fatigue remains the most frequently cited MPN symptom (ET, 90.3%; PV, 91.7%; MF, 98.9%) and is multifactorial in origin. Best researched in myelofibrosis, the symptom manifests in both early and subclinical stages, spanning a wide spectrum of disease severity. Anemia may be a contributor and occurs in MF patients via splenic sequestration, insufficient production of erythropoietin and increased production of cytokines including IL-1, IL-6 and TNF-alpha [7]. Deconditioning is an additional source, correlating with patient functional capacities and disease type. Indeed, activity levels demonstrated by metabolic equivalents (METs) in MPN patients remain significantly compromised in comparison to those observed within healthy controls (25.1 vs. 45.8) and rivals those observed in Parkinson's patients [2]. In PV and ET, fatigue may secondarily result from microthrombosis within the pulmonary vasculature as well as pain related to splenic sequestration and thrombosis.