Relevance of Weight Loss, Splenomegaly, and Hypocholesterolemia in the Treatment of Myeloproliferative Neoplasms—Implications for a *JAK2* Inhibitor Era

Robyn M Scherber, MPH[1] and Ruben A Mesa, MD[2]

1. Medical Student, Chicago Medical School, Rosalind Franklin University of Medicine and Science;
2. Consultant Hematologist and Chair, Department of Hematology and Oncology, Mayo Clinic

Abstract

Myeloproliferative neoplasms (MPNs) encompass a diverse yet homogenous classification of hematologic malignancies including primary myelofibrosis (MF), essential thrombocythemia (ET), and polycythemia vera (PV). Although clinically distinct, these three entities share similar clinical and prognostic features and are characterized by clonal stem cell proliferation with recurrent chromosomal abnormalities. MPNs can be accompanied by symptomatic worsening, particularly weight loss and splenomegaly. However, of these symptoms only splenomegaly is targeted by conventional therapy. With the key discovery of the JAK2V617F mutation, there has been renewed focus on effective treatment strategies aimed at counteracting the debilitating side effects accompanying this disease. In this brief article, we describe the clinical features, course, treatment approaches, and monitoring utility of progressive splenomegaly and cachexia in MPNs.

Keywords

Myeloproliferative neoplasm (MPN), weight loss, splenomegaly, hypocholesterolemia

Disclosure: The authors have no conflicts of interest to declare.
Received: March 18, 2010 **Accepted:** January 19, 2011 **Citation:** *US Oncology & Hematology*, 2011;7(1):61–3 *DOI: 10.17925/OHR.2011.07.1.61*
Correspondence: Ruben A Mesa, MD, Chair, Division of Hematology and Oncology, Mayo Clinic, Scottsdale, AZ 85259. E: mesa.ruben@mayo.edu

Splenomegaly and Cachexia—Presentation and Burden in Myeloproliferative Neoplasms

Myeloproliferative neoplasms (MPNs) are accompanied by a profound clinical profile that significantly reduces overall patient survival and quality of life.[1,2] Epidemiologically, MPNs occur in approximately six per 100,000 individuals and are commonly diagnosed in the fifth decade of life or later.[3] Secondary conditions related to this disease include non-refractory thrombocytosis in essential thrombocythemia (ET), polycythemia in polycythemia vera (PV), and anemia in myelofibrosis (MF).[4] Although unique diagnoses in and of themselves, ET, PV, and MF often share overlapping features and frequently terminate in acute peripheral leukoerythroblastosis with bone marrow fibrosis, extramedullary hematopoiesis, and severe anemia (overt MF or post-ET/PV MF). MPNs, particularly MF, are accompanied by severe constitutional symptoms including weight loss, night sweats, fevers, pruritus, and fatigue, and is complicated by hemorrhages, thrombosis, and splenomegaly.[5] Mortality related to these diseases often results from severe infections, post-splenectomy complications, bleeding, or progression to acute leukemia.

Splenomegaly is a well-described complication of MPNs and likely represents likely splenic sequestration of immature myeloid cells released from the marrow. Splenic hemorrhages, infarcts, infections, and cytopenias resulting from intra-splenic sequestration of blood components are not uncommon.[4] Splenomegaly (>10cm below left costal margin) has been well correlated with cachexia and significant morbidity.[6] Associated hepatomegaly may be massive (>10kg) and secondarily may contribute to the development of portal hypertension, early satiety, bloating, and edema. Between 15 and 81% of patients will present with a palpable spleen at diagnosis that may enlarge during disease progression.[6] Current therapeutic options such as hydroxyurea and lenalidomide can sometimes palliate splenic enlargement.[7] Splenectomy can be considered in patients with severe anemia, thrombocytopenia, and constitutional symptoms, and is associated with significant surgical morbidity (31%) and mortality (9%).[4] Although not exclusive, splenomegaly is most profound in MF patients.[6]

Weight Loss and Cholesterol—Relationships in Myeloproliferative Neoplasms

Weight loss is another well-described feature of MPNs. Stemming from a chronic state of hypercatabolism, cachexia has been found to be a predictor of poor survival in MF[8] and correlates significantly with fatigue.[5] Approximately 13% of MPN patients endorse experiencing undesired weight loss during the course of their disease, with MF encompassing the highest proportion of weight loss (20%) followed by PV or ET (10 and 7%, respectively).[5] Analysis of the Mayo database of patients with MF revealed that 67% of patients lost weight over time, with approximately 27% of patients dropping at least one body mass index (BMI) category.[9]

Table 1: Drugs Being Tested in Myeloproliferative Neoplasms with Activity Against *JAK2*

Drug	Company	Indication	Phase	Class	Reference
INCB018424	Incyte	MF	III	*JAK1* and *2*	32
		PV-ET	II	inhibitor	33
SB1518	SBio	MF	II	*JAK2* inhibitor	34
TG101348	Targen	MF	II	*JAK2* inhibitor	35
LBH589	Novartis	MF	II	HDAC inhibitor	36
RAD001	Novartis	MF	II	mTOR inhibitor	37
CEP-701	Cepahalon	MF	II	*FLT3* and	38
		PV-ET	II	*JAK2* inhibitor	39

ET = essential cytothemia; FLT3 = fetal liver tyrosine kinase 3; HDAC = histone deacetylase; JAK = Janus-activated kinase; MF = myelofibrosis; mTOR = mammalian target of rapamycin; PV = polycythemia vera.

When considering overall weight loss in MPN, confounding variables of edema and spleen size must be taken into account as they may conceal ectomorphic body mass. Additionally, weight loss does not directly correlate with decreased adipose tissue, but rather may represent substantial muscle catabolism. As such, classification of a previously overweight patient into a 'normal' category may underestimate the true degree of muscle catabolism that has occurred.[9]

Inadequate serum cholesterol has long been known to be a feature of MPNs.[10] Despite adequate nutritional status, patients with MPN are more likely to be deficient in low-density lipoprotein cholesterol (LDL-C) (<100mg/dl) and total cholesterol (<150mg/dl) compared with age-matched controls.[11] Data in terms of high-density lipoprotein-cholesterol (HDL-C) (>60mg/dl) in MPN patients appear to change over time, with some studies indicating increased HDL (>60mg/dl) at the time of diagnosis[11] but decreased HDL with progressive disease.[6,10,12] Hypocholesterolemia is exacerbated with untreated disease progression[10] and is correlated with decreased weight.[9] Given that the most frequent variable associated with hypocholesterolemia is splenomegaly, the mechanism for decreased triglycerides may be similar in nature to the cytopenic effect seen with blood components, namely sequestration within the spleen with disease-induced hypercatabolism. Interestingly, there is no available evidence to suggest that the reduction in lipid profiles translates into cardioprotection. Rather, this effect is most likely a measure of disease-related cachexia, which correlates significantly with a poorer prognosis.[11] The effect of hypocholesterolemia is more pronounced in MF compared with PV or ET.[6]

Impact of Therapy on Cachexia and Hypocholesterolemia in Myeloproliferative Neoplasms

Historically, treatment approaches in MPNs have remained focused on palliation of symptoms, primarily through surgical splenectomy and transfusions.[12] Overall, few therapies are available to treat mild forms of disease, and there is much off-label use of therapeutics found clinically to be palliative. Currently, no commercially available agents appear to affect either the cachexia or hypocholesterolemia observed with MPNs, particularly MF.

Splenomegaly can significantly affect quality of life and remains a major target for symptom reduction. The mainstay of treatment for mild to moderate enlargement should include agents with minimal toxicity profiles including oral myelosuppressive agents (hydroxyurea[13]), oral alkylators (melphalan[14] and busulfan[15]), immunomodulatory drugs (thalidomide,[16] lenalidomide,[17] pomalidomide,[18] and thalidomide with steroid[19]), and cytoreductive agents (interferon alpha[20]). Patients who develop severe splenomegaly or extramedullary hematopoiesis should be considered for treatment with purine nucleoside analogs (2-chlorodeoxyadenosine[21]) or hypomethylating agents (azacytidine[22,23] and decitabine[24]). In refractory cases, acute leukemia therapies including cytarabine or daunorubicin could be considered, but these therapies have had little clinical testing and should be considered only when clinical trials are not a viable option.[7,25,26] To date, stem cell transplantation remains the only potentially curative therapy in the treatment of MPNs, but should be offered only to a limited population of MPN patients with aggressive forms of disease.[26–28]

JAK2 Inhibitors Have an Impact on Cachexia in Myelofibrosis

The discovery of the *JAK2* mutation in 2005 was a landmark development in the treatment of MPNs. This gene marker provided concrete evidence of the common link in PV, ET, and MF, and provided researchers with a new therapeutic target capable of directly inhibiting cellular proliferation. Continued research has yielded promising new therapeutics capable of inhibiting the *JAK2* gene's proliferative effects *in vitro*. Currently, 16 *JAK2* inhibitors are under review in clinical trials, with the main agents in testing described in *Table 1*.[26]

Despite their potential, it can be said with certainty that these medications will require extensive investigations. Although mechanistically promising, testing with the prototypic compound furthest through development, INCB018424 (Incyte Corporation, Wilmington, DE), did not appear to attenuate the cytopenias or histologic changes common to MPNs.[29] It did, however, reduce the chronic inflammatory state associated with disease[30] and improve qualitative symptoms.[31] Early data suggest that administration of INCB18424 in MF patients results in dose-dependent improvement in bodyweight gain after treatment (1.75kg increase in bodyweight versus 4kg increase in bodyweight with 25mg twice a day 90 days post-treatment).[31] Increased bodyweight was observed in patients in both the highest and lowest quartiles, indicating a positive effect on weight regardless of the initial BMI (6.5kg weight gain in lowest BMI quartile versus 2kg weight gain in highest BMI quartile).[31] INCB18424 treatment was also associated with a significant increase in total cholesterol (100mg/dl baseline versus 125mg/dl at the final treatment cycle). Remarkably, serum levels of leptin, a neuropeptide associated with satiety, was elevated within 50 days of INCB treatment and was sustained above baseline throughout the course of treatment. High doses at 25mg twice per day resulted in a reduction in early satiety and cachexia in cases of splenomegaly.[31]

With the substantial number of *JAK2* kinase inhibitors in development, more accurate methods to evaluate drug efficacy are required. The effectiveness of INCB18424 in reducing many symptoms associated with MPNs suggests that these medications hold the potential to evolve as standard treatment. It is very possible that many of the inhibitors of *JAK2* (see *Table 1*) may have clinical activity not only against splenomegaly but also against the cachexia and hypocholesterolemia of disease.

Future Directions

MPN symptomology merits continued investigation. The detrimental impact of MPNs on quality of life and overall poor prognosis have resulted in further research into novel therapeutic agents capable of targeting more than palliative symptoms. The new class of *JAK2* inhibitors appears efficacious in early clinical trials in reducing splenomegaly associated with disease as well as reducing cachexia and hypocholesterolemia. With a variety of *JAK2* inhibitors beginning to enter clinical trials, there is potential for successful MPN symptom reduction, which may translate into improved quality of life for MPN patients. ■

1. Dupriez B, Morel P, Demory JL, et al., Prognostic factors in agnogenic myeloid metaplasia: a report on 195 cases with a new scoring system, *Blood*, 1996;88(3):1013–8.
2. Passamonti F, Rumi E, Pungolino E, et al., Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia, *Am J Med*, 2004;117(10):755–61.
3. Mesa RA, Silverstein MN, Jacobsen SJ, et al., Population-based incidence and survival figures in essential thrombocythemia and agnogenic myeloid metaplasia: an Olmsted County Study, 1976–1995, *Am J Hematol*, 1999;61(1):10–5.
4. Tefferi A, Myelofibrosis with myeloid metaplasia, *N Engl J Med*, 2000;342(17):1255–65.
5. Mesa RA, Niblack J, Wadleigh M, et al., The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients, *Cancer*, 2007;109(1):68–76.
6. Mesa RA, Schwager S, Huang J, et al., Weight Loss, Splenomegaly, and Hypocholesterolemia in Myeloproliferative Neoplasms: Patterns and Relevance from the Pre JAK2 Inhibitor Era, *Blood*, 2009;114:3918, *ASH Annual Meeting Abstracts*, New Orleans, LA, December 7, 2009.
7. Mesa RA, How I treat symptomatic splenomegaly in patients with myelofibrosis, *Blood*, 2009;113:5394–400.
8. Varki A, Lottenberg R, Griffith R, et al., The syndrome of idiopathic myelofibrosis. A clinicopathologic review with emphasis on the prognostic variables predicting survival, *Medicine*, 1983;62(6):353–71.
9. Mesa RA, Schwager S, Huang J, et al., Dynamics, and prognostic impact, of weight loss in primary myelofibrosis, *Blood*, 2008;112(11):5224.
10. Gilbert HS, Ginsberg H, Fagerstrom R, et al., Characterization of hypocholesterolemia in myeloproliferative disease. Relation to disease manifestations and activity, *Am J Med*, 1981;71(4):595–602.
11. Mesa RA, Huang J, Schwager S, et al., Hypocholesterolemia Is Independently Associated with Decreased Survival in Patients with Primary Myelofibrosis: An Analysis of Lipid Profiles in 558 Myeloproliferative Patients, *Blood*, 2007;110(11):2548.
12. Kiss A, Telek B, Rak K, Hypocholesterolemia and other lipoprotein disorders in myelofibrosis, *Orvosi Hetilap*, 1994;135(48):2643–6.
13. Lofvenberg E, Wahlin A, Management of polycythaemia vera, essential thrombocythaemia and myelofibrosis with hydroxyurea, *Eur J Haematol*, 1988;41(4):375–81.
14. Petti MC, Latagliata R, Spadea T, et al., Melphalan treatment in patients with myelofibrosis with myeloid metaplasia, *Br J Haematol*, 2002;116(3):576–81.
15. Manoharan A, Pitney WR, Chemotherapy resolves symptoms and reverses marrow fibrosis in myelofibrosis, *Scand J Haematol*, 1984;33(5):453–9.
16. Barosi G, Elliot M A, Canepa L, et al., Thalidomide in myelofibrosis with myeloid metaplasia: a pooled analysis of individual patient data from five studies, *Leukemia Lymphoma*, 2002;43(12):2301–7.
17. Tefferi A, Cortes J, Verstovsek S, et al., Lenalidomide therapy in myelofibrosis with myeloid metaplasia, *Blood*, 2006;108:1158–64.
18. Tefferi A, Verstovsek S, Barosi G, et al., Pomalidomide therapy in anemic patients with myelofibrosis: results from a phase-2 randomized multicenter study, *Blood*, 2008;112(11):663.
19. 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(7):2534–41.
20. Levy B, Vandris K, Adriano F, et al., Recombinant Interferon Alpha (rIFN{alpha}) May Retard Progression of Early Primary Myelofibrosis (PM) by Reducing Splenomegaly and by Changing Marrow Morphology, *Blood*, 2008;112(11):1758, *ASH Annual Meeting Abstracts*, San Francisco, CA, November 16, 2008.
21. Faoro LN, Tefferi A, Mesa RA, Long-term analysis of the palliative benefit of 2-chlorodeoxyadenosine for myelofibrosis with myeloid metaplasia, *Eur J Haematol*, 2005;74(2):117–20.
22. Quintás-Cardama A, Tong W, Kantarjian H, et al., A phase II study of 5-azacitidine for patients with primary and post essential thrombocythemia/polcythemia vera myelofibrosis, *Leukemia*, 2008;22:965–70.
23. Mesa RA, Verstovsek S, Rivera C, et al., 5-Azacitidine has limited therapeutic activity in myelofibrosis, *Leukemia*, 2009;23(1):180–2.
24. Danilov AV, Relias V, Feeney DM, et al., Decitabine is an effective treatment of idiopathic myelofibrosis, *Br J Haematol*, 2009;145(1):131–2.
25. Tefferi A, Barbui T, bcr/abl-negative, classic myeloproliferative neoplasms: diagnosis and treatment, *Mayo Clin Proc*, 2005;80(9):1220–32.
26. Mesa RA, Tefferi A, Emerging drugs for the therapy of primary and post essential thrombocythemia, post polycythemia vera myelofibrosis, *Exp Opin Emerg Drugs*, 2009;14(3):471–9.
27. Mesa RA, New insights into the pathogenesis and treatment of chronic myeloproliferative disorders, *Curr Opin Hematol*, 2008;15(2):121–6.
28. Deeg HJ, Gooley TA, Flowers ME, et al., Allogeneic hematopoietic stem cell transplantation for myelofibrosis, *Blood*, 2003;102(12):3912–8.
29. Mesa RA, New drugs for the treatment of myelofibrosis, *Curr Hematol Malignancy Rep*, 2010;5(1):15–21.
30. Tefferi A, Kantarjian HM, Pardanani AD, et al., The clinical phenotype of myelofibrosis encompasses a chronic inflammatory state that is favorably altered by INCB018424, a selective inhibitor of JAK1/2, *Blood*, 2008;112(11):2804, *ASH Annual Meeting Abstracts*, San Francisco, CA, November 16, 2008.
31. Mesa RA, Verstovsek S, Kantarjian HM, et al., INCB018424, a selective JAK1/2 inhibitor, significantly improves the compromised nutritional status and frank cachexia in patients with myelofibrosis (MF), *Blood*, 2008;112(11):1760, *ASH Annual Meeting Abstracts*, San Francisco, CA, November 16, 2008.
32. Verstovsek S, Kantarjian H, Mesa RA, et al., Long-term follow up and optimized dosing regimen of INCB018424 in patients with myelofibrosis: durable clinical, functional and symptomatic responses with improved hematological safety, *Blood*, 2009;114(22):756, *ASH Annual Meeting Abstracts*, New Orleans, LA, December 7, 2009.
33. Verstovsek S, Passamonti F, Rambaldi A, et al., A phase 2 study of INCB018424, an oral, selective JAK1/JAK2 inhibitor, in patients with advanced polycythemia vera (PV) and essential thrombocythemia (ET) refractory to hydroxyurea, *Blood*, 2009;114(22):311, *ASH Annual Meeting Abstracts*, New Orleans, LA, December 7, 2009.
34. Verstovsek S, Odenike O, Scott B, et al., Phase I dose-escalation trial of SB1518, a novel JAK2/FLT3 inhibitor, in acute and chronic myeloid diseases, including primary or post-essential thrombocythemia/polycythemia vera myelofibrosis, *Blood*, 2009;114(22):3905, *ASH Annual Meeting Abstracts*, New Orleans, LA, December 7, 2009.
35. Pardanani AD, Gotlib JR, Jamieson CJ, et al., A phase I evaluation of TG101348, a selective JAK2 inhibitor, in myelofibrosis: clinical response is accompanied by significant reduction in JAK2V617F allele burden, *Blood*, 2009;114(22):755, *ASH Annual Meeting Abstracts*, New Orleans, LA, December 7, 2009.
36. Mascarenhas J, Wang X, Rodriguez A, et al., A phase I study of LBH589, a novel histone deacetylase inhibitor in patients with primary myelofibrosis (PMF) and post-polycythemia/essential thrombocythemia myelofibrosis (post-PV/ET MF), *Blood*, 2009;114(22):308, *ASH Annual Meeting Abstracts*, New Orleans, LA, December 7, 2009.
37. Vannucchi AM, Guglielmelli P, Gattoni E, et al., RAD001, an Inhibitor of mTOR, shows clinical activity in a phase I/II study in patients with primary myelofibrosis (PMF) and post polycythemia vera/essential thrombocythemia myelofibrosis (PPV/PET MF), *Blood*, 2009;114(22):307, *ASH Annual Meeting Abstracts*, New Orleans, LA, December 7, 2009.
38. Hexner E, Goldberg JD, Prchal JT, et al., A multicenter, open label phase I/II study of CEP701 (lestaurtinib) in adults with myelofibrosis; a report on phase I: a study of the myeloproliferative disorders research consortium (MPD-RC), *Blood*, 2009;114(22):754, *ASH Annual Meeting Abstracts*, New Orleans, LA, December 7, 2009.
39. Moliterno AR, Hexner E, Roboz GJ, et al., An open-label study of CEP-701 in patients with JAK2 V617F-positive PV and ET: update of 39 enrolled patients, *Blood*, 2009;114(22):753, *ASH Annual Meeting Abstracts*, New Orleans, LA, December 7, 2009.