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

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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

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. Epidemiologically, MPNs occur in approximately six per 100,000 individuals and are commonly diagnosed in the fifth decade of life or later. Secondary conditions related to this disease include non-refractory thrombocytosis in essential thrombocythemia (ET), polycythemia in polycythemia vera (PV), and anemia in myelofibrosis (MF). 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. 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. Splenomegaly (>10cm below left costal margin) has been well correlated with cachexia and significant morbidity. 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. Current therapeutic options such as hydroxyurea and lenalidomide can sometimes palliate splenic enlargement. Splenectomy can be considered in patients with severe anemia, thrombocytopenia, and constitutional symptoms, and is associated with significant surgical morbidity and mortality. Although not exclusive, splenomegaly is most profound in MF patients.

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 and correlates significantly with fatigue. 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). 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.
Table 1: Drugs Being Tested in Myeloproliferative Neoplasms with Activity Against JAK2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Indication</th>
<th>Phase</th>
<th>Class</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCBO18424</td>
<td>Incyte</td>
<td>MF</td>
<td>III</td>
<td>JAK1 and 2 inhibitor</td>
<td>32</td>
</tr>
<tr>
<td>SB1518</td>
<td>SBio</td>
<td>MF</td>
<td>II</td>
<td>JAK2 inhibitor</td>
<td>34</td>
</tr>
<tr>
<td>TG101348</td>
<td>Targen</td>
<td>MF</td>
<td>II</td>
<td>JAK2 inhibitor</td>
<td>35</td>
</tr>
<tr>
<td>LBHS89</td>
<td>Novartis</td>
<td>MF</td>
<td>II</td>
<td>HDAC inhibitor</td>
<td>36</td>
</tr>
<tr>
<td>RAD001</td>
<td>Novartis</td>
<td>MF</td>
<td>II</td>
<td>mTOR inhibitor</td>
<td>37</td>
</tr>
<tr>
<td>CEP-701</td>
<td>Cepahalon</td>
<td>MF</td>
<td>II</td>
<td>FLT3 and JAK2 inhibitor</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PV-ET</td>
<td></td>
<td></td>
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</tr>
</tbody>
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ET = essential cytopenia; FLT3 = feral (ery) 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.

Inadequate serum cholesterol has long been known to be a feature of MPNs. 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. 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 but decreased HDL with progressive disease. Data in terms of high-density lipoprotein-cholesterol (<100mg/dl) and total cholesterol (<150mg/dl) compared with age-matched controls. 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. 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 but decreased HDL with progressive disease.

Hypocholesterolemia is exacerbated with untreated disease progression and is correlated with decreased weight. 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. The effect of hypocholesterolemia is more pronounced in MF compared with PV or ET.

**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. 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), oral alkylators (melphalan and busulfan), immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide, and thalidomide with steroids), and cytoreductive agents (interferon alpha). Patients who develop severe splenomegaly or extramedullary hematopoiesis should be considered for treatment with purine nucleoside analogs (2-chlorodeoxyadenosine) or hypomethylating agents (azacytidine and decitabine). 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. 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.

### 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.

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, INCBO18424 (Incyte Corporation, Wilmington, DE), did not appear to attenuate the cytopenias or histologic changes common to MPNs. It did, however, reduce the chronic inflammatory state associated with disease and improve qualitative symptoms. Early data suggest that administration of INCBO18424 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). 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). INCBO18424 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 INCBO18424 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.

With the substantial number of JAK2 kinase inhibitors in development, more accurate methods to evaluate drug efficacy are required. The effectiveness of INCBO18424 in reducing many symptoms associated with MPNs suggests that these medications hold the potential to evolve as standard treatment. It is very likely 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 hypcholesterolemia. 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.