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Case report

Surprising results of a supportive integrated therapy in myelofibrosis

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ABSTRACT

Objectives: Myelofibrosis (MF) is characterized by shortened survival and a greatly compromised quality of life. Weight loss and cachexia seem to be the most important factors influencing survival in patients with MF. The aim of this study was to assess the efficacy of an integrated supportive therapy in improving cachexia and MF-related symptoms.
Methods: We reported on a case of a patient with MF who presented with weight loss and cachexia associated with severe anemia, fatigue, fever, and bone pain. The circulating levels of inflammatory, oxidative stress parameters, hepcidin, and erythropoietin were evaluated and were above normal ranges. The patient was treated with a multitargeted approach specifically developed for cachexia including oral L-carnitine, celecoxib, curcumin, lactoferrin, and subcutaneous recombinant human erythropoietin (EPO)-α.
Results: Surprisingly, after 1 y, cachexia features improved, all MF symptoms were in remission, and inflammatory and oxidative stress parameters, hepcidin, and EPO were reduced.
Conclusions: Because our protocol was targeted at inflammation and the metabolic state, its effectiveness may emphasize the role of inflammation in the pathogenesis of MF symptoms and demonstrates a need for the study of new integrated therapeutic strategies.

Introduction

Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by clonal myeloproliferation, ineffective erythropoiesis, bone marrow stromal changes, hepatosplenic extramedullary hematopoiesis, and aberrant cytokine expression [1].

Patients with MF have a shortened life span and a greatly compromised quality of life (QoL) [2]. Weight loss and cachexia seem to be the most important factors related to survival in patients with MF [3]. Just as important is the substantial MF-associated symptom burden, which includes severe anemia (often requiring red blood cell [RBC] transfusions), symptomatic enlargement of the spleen and liver, fatigue, weakness, abdominal pain, pruritus, fever, night sweats, and bone pain [4].

An important role in the pathogenesis of the MF involves the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. Aberrant JAK/STAT pathway activity is involved in the regulation of proliferation and the differentiation of hematopoietic cells in MF [5]. This condition leads to the hyperactivation of the JAK/STAT pathway and the subsequent activation of downstream signaling networks.

Hematopoietic stem cell transplantation is the only potentially curative treatment. The value of drug therapy is mostly palliative [6]. New targeted JAK inhibitor therapies, such as ruxolitinib, are now available. Ruxolitinib, compared with placebo or the best available therapy, provides significant clinical benefits in patients with MF by reducing spleen size and ameliorating debilitating MF-related symptoms [7,8]. Furthermore, it has been suggested that ruxolitinib may improve patient survival by improving their nutritional status [9].

Methods

A 63-y-old man diagnosed with MF was referred to our clinic for observation. A bone marrow biopsy revealed dishomogeneous bone marrow cellularity with a predomination of areas with bone marrow aplasia (~5% in most cellulated areas), a normal ratio of myeloid to erythroid M:E = 3:1 and focal myelosclerosis

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with severe MF (2+). The hematologist made the judgment that the patient was not a candidate for any specific MF therapy and submitted him to our attention to plan the best supportive therapy.

The patient presented with weight loss (~10 kg in the previous 6 mo), cachexia associated with severe anemia (hemoglobin [Hb], 78 g/L) that required blood transfusion, fatigue, weakness, fever (39°C), and bone pain. He had a positive history for type 2 diabetes mellitus, hypertension, and ischemic heart disease. Both his diabetes and cardiac disease were well controlled at the time of observation. The initial physical examination revealed splenomegaly. At baseline, a computed tomography (CT) scan showed splenomegaly with a longitudinal diameter of 17 cm.

The laboratory assays revealed the following: RBC 3.15 × 10^{12}/L; white blood cells 3.85 × 10^{9}/L; mean cell volume 80.8 fl; platelets 176 × 10^{9}/L; ferritin 1186 pmol/L; serum iron 8.4 μmol/L; lactate dehydrogenase 314 U/L; and C-reactive protein (CRP) 51.7 mg/L (Table 1).

As biological markers, we also evaluated at baseline and every 3 mo the following: circulating levels of the proinflammatory cytokines interleukin (IL)-6 and tumor necrosis factor (TNF)-α, hepcidin, erythropoietin (EPO), leptin, and reactive oxygen species (ROS) (Table 1). Baseline elevations (in comparison to normal range) of CRP, IL-6, TNF-α, hepcidin, EPO, and ROS were observed. The patient's leptin level (adjusted for body mass index) was below the normal range for healthy individuals of normal weight. We began evaluating plasma leptin in our previous studies as a marker of energy consumption and anorexia strictly in relation to weight loss and inflammation [10].

Considering the clinical picture and the major effects of the symptoms associated with cachexia, we have developed a multitargeted treatment approach including oral L-carnitine 2 g/d, celecoxib 100 mg/d, curcumin (Meriva®, Indena, Milan, Italy) 4 g/d, lactoferrin 200 mg/d, and subcutaneous recombinant human EPO (rHuEPO)-α 30000 UI/w. The patient provided written informed consent for the protocol, which was performed after approval of local institutional review board.

Rationale for treatment plan

The agents included in our combined treatment approach have been selected on the basis of our previously published studies carried out in patients with cancer cachexia [11,12] with the following rationale. L-Carnitine plays a pivotal role in modulating cell energy metabolism [13]. The cyclooxygenase-2 inhibitor celecoxib is able to inhibit the inflammatory process and has an effect on weight loss [14]. Curcumin was included for its anti-inflammatory and antioxidant actions; however, we did not disregard the fact that it is currently one of the most well-evaluated nutraceutical products and has been shown to have specific actions on the nuclear factor-κB and JAK-STAT pathway and the synthesis of proinflammatory cytokines, which is dependent on those pathways [15]. rHuEPO was chosen for its known ability to improve Hb levels in patients affected by MF [16,17]. In view of the current debate on the necessity of associating intravenous iron with rHuEPO whenever ferritin levels are high as a consequence of functional iron deficiency due to chronic inflammation, we choose to include lactoferrin in this treatment approach; as we have previously demonstrated, lactoferrin has the ability to modulate iron metabolism in anemic advanced cancer patients [18].

Laboratory parameters and MF symptom evaluation

Parameters related to cancer cachexia [19], for example, body weight, lean body mass (LBM) measured by dual-energy X-ray absorptiometry (DXA) using a Hologic Delphi W scanner (Hologic Inc., Bedford, MA, USA), appetite by visual analog scale (VAS), fatigue by the multidimensional fatigue symptom inventory-short form (MFSI-SF), and global QoL using the European Organization for Research and Treatment of Cancer Quality of Life 30 Questionnaire (EORTC QLQ-C30) were assessed every 3 mo. Whole-body DXA scans use the differential attenuation of two low-dose X-ray beams at 70 and 140 keV, respectively, to partition total body mass into bone, lean and fat soft tissue components based on established mass to attenuation constants for bone mineral, and lipid [20]. A trained technologist performed measurements. The MSFI-SF, a self-administered questionnaire, consists of 30 items designed to assess the multidimensional nature of fatigue. The highest MFSI- SF scores are associated with higher fatigue levels [21]. The EORTC QLQ-C30 is a 30-item, cancer-specific, self-reporting questionnaire including five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, pain, and nausea/vomiting), two items assessing global health and QoL and a number of single items addressing various symptoms (constipation, diarrhea, dyspnea, anorexia, and insomnia), and perceived financial impact. The results were transformed into standardized scores ranging from 0 to 100 [22].

Circulating levels of the proinflammatory cytokines IL-6 and TNF-α, hepcidin, EPO, and leptin assessed by enzyme-linked immunosorbent assay were assessed using commercial kits (DRG Instruments GmbH, Marburg, Germany). At 08:00 h, following an overnight fast, blood samples for these analyses were collected in tubes with a clot-activating factor, centrifuged immediately after collection, and the serum was stored at −20°C until assayed in the same batch. The coefficient of variation for these methods was <5%, as established by routine quality control procedures. ROS were assessed in fresh blood sample by the FORT test (Callegari, Parma, Italy), which is a colorimetric assay able to measure the radical species produced by transitional metals (i.e., iron) proportionally to lipid peroxides present in the blood sample. The addition of a p-phenylenediamine derivative forms a radical molecule that can be evaluated with spectrophotometry at 505 nm (Form CR 2000, Callegari, Parma, Italy). Results were expressed as FORT units, where 1 FORT unit corresponds to 0.26 mg/L of hydrogen peroxide. The assay was CE marked for diagnostic use. The manufacturer instructions were followed. The coefficient of variation was <5%, as established by internal quality control procedures [23].

Every 3 mo, MF symptoms were evaluated using the modified Myelofibrosis Symptom Assessment Form v2.0 diary (total symptom score). Routine hematologic parameters were evaluated weekly for the first 3 mo and then every month throughout the rest of the treatment course. Spleen size was assessed by CT scan at baseline and after 1 y of treatment.

Table 1
Baseline laboratory parameters

Parameter	Value	Normal range
RBC (1 × 10^{12}/L)	3.15	4.30–5.20
WBC (1 × 10^{9}/L)	3.85	4.00–10.00
MCV (fl)	80.8	80–99
PLT (1 × 10^{9}/L)	176	150–450
Serum iron (μmol/L)	8.4	7.2–25.9
Ferritin (ng/mL)	528	11–306.8
LDH (U/L)	314	266–500
CRP (mg/L)	51.7	<10
IL-6 (pg/mL)	21.94	0–4
TNF-α (pg/mL)	16.84	0–14
Hepcidin (ng/mL)	89	1–40
EPO (U/l)	230.6	2–20
Leptin (ng/mL)	0.1	4–20
ROS (FORT U)	510	<320

CRP, C-reactive protein; EPO, erythropoietin; IL, interleukin; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; PLT, platelet; RBC, red blood cell; ROS, reactive oxygen species; TNF, tumor necrosis factor; WBC, white blood cell

Results

The treatment was administered for 1 y. Patient compliance was optimal. The treatment was well tolerated and no side effects have been reported. The combined regimen was effective in improving several important features of cachexia (i.e., body weight, LBM, fatigue, and global QoL; Fig. 1). In detail, the patient experienced a progressive increase in body weight over time, with an increase of 2 kg at 3 mo, 4 kg at 6 mo, and 8 kg at 1 y. LBM was increased by 6.1 kg after 1 y of treatment. Additionally, fatigue decreased by 37% by month 2 and continued to improve throughout the first year of treatment (−82%). The evaluation of global QoL by the EORTC QLQ-C30 demonstrated an 80% improvement from baseline.

Consistently over the treatment period, these improvements were associated with a reduction in serum levels of CRP, the proinflammatory cytokines TNF-α and IL-6, hepcidin, and ROS (Table 2 and Fig. 2). The patient's serum leptin levels were increased at month 2, and the increase continued over the remainder of the treatment period (Table 2 and Fig. 2). The leptin increase paralleled with body weight increase and may reflect an improvement in the patient's metabolic efficiency.

Symptoms more specific to MF improved rapidly, and that improvement was maintained over the 1-y treatment period (Fig. 1). In particular, the patient realized a decrease in bone pain that started at month 1 (−37%), and at 1 y after the initiation of this treatment, the patient reported an absence of pain (−100%). The patient's fever disappeared during the treatment at month 1