Letters

A Multitargeted Treatment Approach for Anemia and Cachexia in Metastatic Castration-Resistant Prostate Cancer

To the Editor:

Localized prostate cancer treated via definitive local therapy becomes metastatic in 30% of cases. Despite a temporary response to androgen deprivation therapy, a castration-resistant prostate cancer (CRPC) requiring further therapy eventually develops.[1] Management of metastatic CRPC can include chemotherapeutic and nonchemotherapeutic agents, depending on disease burden and patient comorbidities.[2] During prostate cancer progression, antineoplastic treatment and tumor-patient interactions may result in anemia, anorexia, and cachexia, which severely compromise patient quality of life (QoL).[3] Herein, we describe a patient with metastatic CRPC and severe anemia associated with fatigue and cachexia successfully treated via an integrated multitargeted supportive approach.

Case

In March 2014, a 78-year-old man was referred for anemia (hemoglobin [Hb] 9.0 g/dL) and profound exhaustion. On initial observation, he also had symptoms suggestive of cachexia/anorexia, nausea, and weight loss (approximately 7% of body weight in the last three months). He had been diagnosed in 1995 with a prostate adenocarcinoma treated with radical prostatectomy plus lymphadenectomy (Stage pT2cN2, Gleason score 7). He received total androgenic blockade until December 2010. Because of biochemical progression and evidence of bone metastases, he suspended antiandrogen therapy and continued only a luteinizing hormone-releasing hormone analogue until December 2011, when his prostate-specific antigen (PSA) level further increased, and CT scan and bone scintigraphy showed progression of bone metastases. He then was enrolled in a double-blind randomized trial of tasquinimod vs. placebo in the Department of Medical Oncology at another hospital. When the patient was referred to us, considering his compromised clinical condition, we contacted the other center and, after their approval, the blinded randomization was opened; we found out that the patient was receiving tasquinimod 1 mg/day. Tasquinimod is an investigational drug that showed therapeutic activity against metastatic CRPC in a Phase II clinical trial[4] and is currently being tested in a Phase III clinical trial. Its antineoplastic activity is mediated by antiangiogenic and immunomodulatory effects.[5] At this point, we hypothesized that the patient's condition was the result of disease progression, or tasquinimod treatment, or both. In fact, a common side effect of tasquinimod is chronic inflammation characterized by anemia, leukocytosis, fatigue, muscular weakness, and increased C-reactive protein (CRP).[5] Moreover, evaluation showed raised PSA levels, and a positron emission tomography scan was indicative for increased metabolic activity in multiple skeletal sites and mediastinal nodes associated with bilateral pleural effusion.

Laboratory assays confirmed the diagnosis of anemia (Hb 9.0 g/dL) and revealed the following: red blood cells 3.27×10^6/mL, mean cell volume 89.6 fL, white blood cells 13.42×10^3/mL, serum iron 25 mg/dL, ferritin 448 ng/mL, and CRP 44.5 mg/L. The hematological results were compatible with a diagnosis of anemia of chronic disease (ACD). According to our protocol for ACD, we evaluated the following parameters: hepcidin, erythropoietin, leptin, albumin, reactive oxygen species (ROS), and the proinflammatory cytokines, that is, interleukin (IL)-6 and tumor necrosis factor (TNF)-α. IL-6, TNF-α, hepcidin, and ROS were above normal ranges. Leptin level, adjusted for body mass index, was below the normal range. Leptin is a marker of energy consumption, and anorexia strictly related to weight loss and inflammation and, as we recently reported,[6] it is useful for characterizing patients with cancer-related anemia. We also evaluated the main parameters defining cachexia,[7] namely, lean body mass, grip strength, fatigue, and QoL, which revealed muscle wasting associated with reduced muscle strength and poor QoL.

Considering the patient's compromised general status and the negative impact of symptoms, we immediately started a multitargeted supportive treatment consisting of oral L-carnitine (2 g/day), curcumin (Meriva®; Indena,

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Milan, Italy; 4 g/day), lactoferrin (200 mg/day), and the cyclooxygenase-2 inhibitor celecoxib (100 mg/day). These agents were chosen on the basis of our previously published data of cancer-related anemia and cachexia.[8] L-carnitine is a central regulator of cell energy metabolism.[9] Celecoxib blocks inflammation and counteracts weight loss.[10] Curcumin is one of the most highly regarded nutraceuticals with both anti-inflammatory and antioxidant actions. It has been shown to specifically inhibit the synthesis of proinflammatory cytokines via the nuclear factor-kappa B and Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathways, which are activated in CRPC patients.[11] Lactoferrin has previously been shown to modulate iron metabolism in anemic advanced cancer patients.[12] The patient provided written informed consent for the protocol after approval by the local institutional review board.

Moreover, because of disease progression in May 2014, the patient stopped tasquinimod and began taking abiraterone acetate 1000 mg/day, an approved treatment for minimally symptomatic chemotherapy-naïve metastatic CRPC patients and also subcutaneous denosumab 120 mg every 28 days, supplemented with calcium and vitamin D.

Between March 2014 (when our multitargeted treatment was initiated) and May 2014 (when tasquinimod was suspended), Hb and iron levels rose, whereas ferritin and CRP dropped (Fig. 1). During the remainder of the treatment, all hematological parameters continued to improve (Fig. 1). The combined treatment also improved several features of cachexia and was associated with reduced TNF-α, IL-6, hepcidin, ROS, and increased leptin levels (Fig. 1). Leptin increase paralleled weight gain and may reflect an improvement in the patient's metabolic efficiency. PSA decreased progressively from 338 to 122 ng/mL. CT scan and bone scintigraphy showed stable disease. The multitargeted treatment was administered continuously for nine months, and

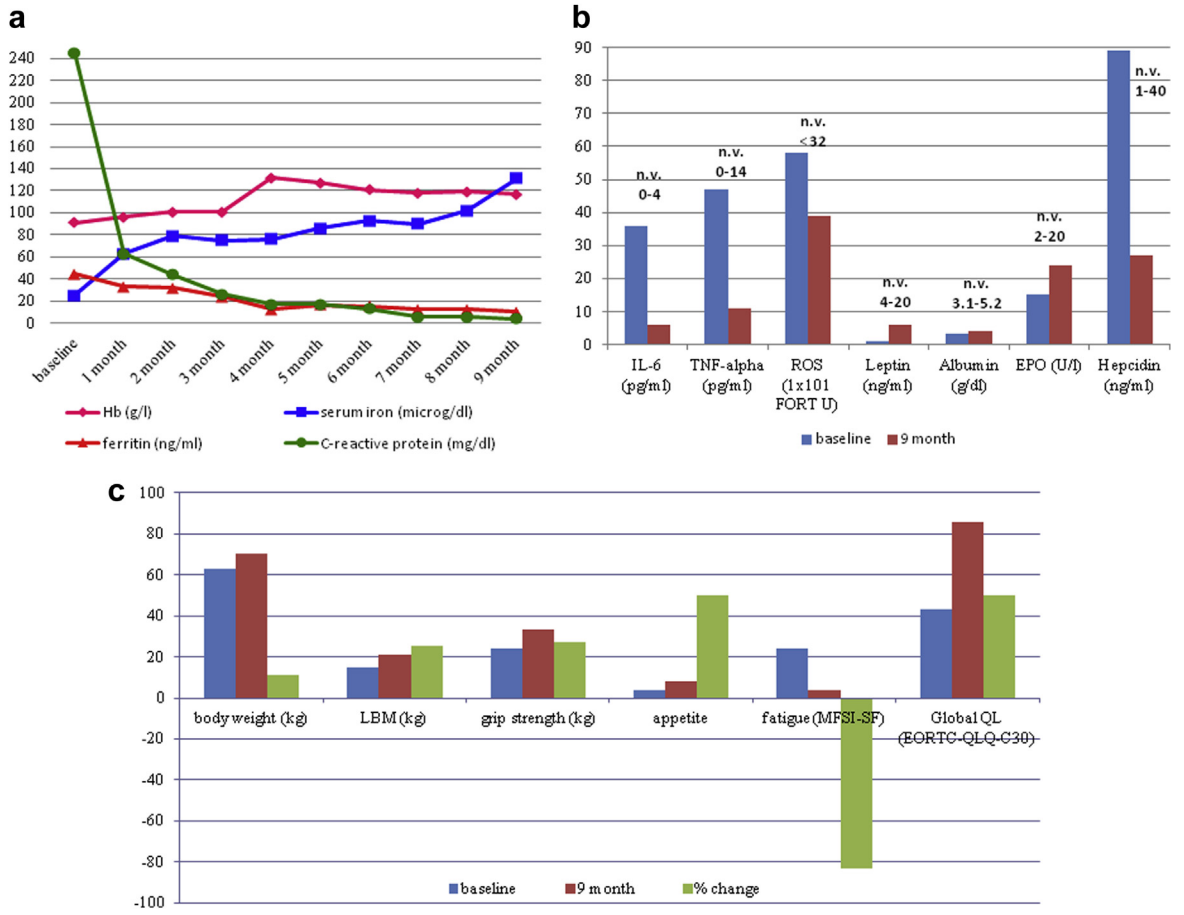

Fig. 1. Changes in laboratory and clinical parameters of anemia and cachexia from baseline to the ninth month of treatment. a) Hb, iron metabolism parameters, and C-reactive protein improved during the treatment period. b) Proinflammatory cytokines, hepcidin, and ROS decreased, whereas EPO, albumin, and leptin decreased from baseline to the ninth month of treatment. c) As for cachexia parameters, the patient experienced a progressive increase in body weight, LBM, and grip strength. Moreover, a decrease of fatigue and an improvement in QoL has been observed. Hb = hemoglobin; IL = interleukin; TNF = tumor necrosis factor; ROS = reactive oxygen species; EPO = erythropoietin; n.v. = normal values; LBM = lean body mass; QoL = quality of life; MFSI-SF = Multidimensional Fatigue Symptom Inventory-Short Form; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire.