Patients With Waldenström Macroglobulinemia Commonly Present With Iron Deficiency and Those With Severely Depressed Transferrin Saturation Levels Show Response to Parenteral Iron Administration

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Abstract

Anemia often prompts therapy in Waldenström macroglobulinemia (WM), although is not fully explained by bone marrow disease involvement in many patients. Hepcidin regulates gut absorption and distribution of iron and is elevated and associated with anemia in WM. Since hepcidin evaluation remains experimental, we initiated an American Board of Internal Medicine (ABIM) practice improvement project to determine baseline transferrin saturation (TSAT) levels in untreated anemic patients with WM. Among 108 patients with WM evaluated, 56 (52%) had a TSAT level ≤ 20%, which included 25 (23%) patients with severely depressed TSAT levels (≤ 10%). Sixteen patients with TSAT levels ≤ 10% received parenteral iron, and 14 of these patients showed improved hematocrit values (28.75% to 32.75%; $P < .0001$), mean corpuscular volume (MCV) (84.7 to 89.9; $P = .006$), and TSAT levels (8.1% to 21.2%; $P < .0001$). Anemia in 8 of these patients was previously refractory to oral iron therapy. Routine screening of iron saturation levels may therefore identify patients with WM and severe iron deficiency who may be candidates for parenteral iron therapy.

Introduction

Anemia is commonly encountered in Waldenström macroglobulinemia (WM) and is considered among the foremost reasons for initiation of therapy.[1] Although bone marrow replacement by disease is an important component for the production of anemia in patients with WM, other causes that may contribute include a dilution effect resulting from the intravascular osmotic draw imposed by high IgM levels, hemolysis resulting from cold as well as warm antibodies, and bone marrow injury inflicted by previous chemotherapy exposure and/or treatment-related myelodysplasia. Despite thorough evaluation for these causes, anemia is often out of proportion to bone marrow disease involvement for many patients with WM.[1]

Hepcidin is a peptide hormone that regulates iron metabolism.[2,3] Although primarily produced by hepatocytes, other cells—including WM lymphoplasmacytic cells, may also produce hepcidin.[3-6] It exerts its regulatory function by binding to and mediating the internalization and subsequent degradation of the iron export protein ferroportin, which is found on enterocytes, monocytes, and macrophages.[7-9] On ligation by hepcidin, ferroportin is internalized, ubiquinated, and degraded. By inhibiting ferroportin, hepcidin blocks the gut from secreting absorbed iron into the hepatic portal system. Iron release from monocytes and macrophages is also prevented by hepcidin, causing buildup of iron stores.

Hepcidin as a potential mediator of anemia in WM was previously investigated by us.[6] Hepcidin levels positively correlated with bone marrow disease involvement and negatively correlated with hemoglobin in all patients with WM. Hepcidin plasma levels for all patients with WM were elevated in comparison with healthy donors. Among 44 patients with WM who presented with anemia, hepcidin levels were higher than in 9 patients with WM who did not have anemia. These patients also showed a trend for more pronounced hypoferremia, with 12 of 44 (27%) patients exhibiting a transferrin saturation (TSAT) level of ≤ 10% vs. 0 of 9 patients without ane-

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mia.[6] Consistent with a hepcidin-mediated effect, morphologic examination after iron staining of bone marrow biopsy samples from patients with WM and elevated hepcidin levels showed an increased hemosiderin presence in macrophages that was absent in erythroblasts in contrast to healthy donors.[6] These observations support the presence of an iron reutilization defect in many patients with WM, as first proposed by Cartwright, wherein anemia results in part from an inadequate release of iron from reticuloendothelial cells despite adequate iron stores.[10,11]

The finding of elevated hepcidin levels and the common presentation of patients with WM and iron deficiency in the small series by Ciccarelli et al suggested to us that an iron-deficient state may commonly exist in patients with WM.[6] Such a finding, therefore, may account in part for the anemia observed in WM, including in patients with discordant bone marrow findings. Since screening for iron deficiency was not recommended in the original consensus guidelines for patients with WM,[12] we instituted an initiative as part of an approved American Board of Internal Medicine (ABIM) practice improvement project wherein all untreated anemic patients with WM would have their TSAT levels determined at baseline. The results of this study are reported in this article.

Patients and Methods

The study was approved by the Dana Farber Cancer Institute/Harvard Cancer Center Institutional Review Board, and the practice improvement project was approved by the ABIM as part of a maintenance of certification project in medical oncology for Dr Treon. As part of this initiative, all patients with a consensus diagnosis of WM[13] who presented from May 1, 1999 to October 1, 2012 to our WM clinic were identified, and metrics were put in place to identify those patients who were untreated at presentation and who had TSAT levels identified before and after the practice improvement initiative. The subsequent impact on patient care after the practice improvement initiative as a consequence of determining baseline TSAT levels was also assessed. Since the evaluation of hepcidin levels is a research tool and not Clinical Laboratory Improvement Amendments approved, the determination of hepcidin levels for these patients was not possible; therefore only TSAT determinations were pursued. TSAT levels were determined by the ratio of total iron to total iron binding capacity (TIBC). The normal reference range for hematocrit values was 34.8% to 43.6% and 38.4% to 48.2% for female and male individuals, respectively, and 37 to 170 μg/dL and 250 to 450 μg/dL for iron and TIBC, respectively. TSAT levels of $\leq$ 10% used to define severe iron deficiency and as the cutoff for recommending parenteral iron infusions.

Results

Of 1413 unique patients seen in our WM clinic from May 1, 1999 to October 1, 2012, 722 were untreated. Among 722 untreated patients, 64 of 278 (23.02%) had TSAT levels determined before the practice improvement initiative vs. 108 of 127 (85.03%) patients after its institution ($P < .00001$ by the Fisher exact test). The baseline characteristics for 108 patients in whom TSAT levels were determined appear in Table 1. Among these patients, 56 (51.9%) had TSAT levels of $\leq$ 20%. This included 25 (23%) patients with severe iron deficiency as defined by a TSAT level $\leq$ 10%. In 10 of these 25 cases, patients had had previous oral iron supplementation without improvement in their hematocrit value, and their disease was deemed to be refractory to oral iron therapy.

Table 1 Baseline Characteristics of 108 Patients With WM for Whom Iron Deficiency Studies Were Performed After Implementation of a Practice Improvement Initiative

Variable	Median	Range
Hematocrit (%)	29.3	19.7-33.0
Serum IgM (mg/dL)	3175	345-8630
Bone Marrow Disease Involvement (%)	50	5-90
Serum Iron Levels (μg/dL)	59	0-264
TIBC (μg/dL)	279	129-1111
TSAT (%)	19.6	0-90.1

Abbreviations: TIBC = total iron binding capacity; TSAT = transferrin saturation; WM = Waldenström macroglobulinemia.

Among the 25 patients with WM who were identified with severe iron deficiency, recommendations for parenteral iron supplementation were made for 20 patients. In 5 cases, patients were enrolled in clinical trials that did not permit interventions with potential impact on hematologic function. In 2 patients, local physicians did not follow through with recommendations, whereas in 2 other cases, patients were lost to follow-up. In total, 16 patients received parenteral iron supplementation with subsequent follow-up in our WM clinic. Patients received a median of 6 (range 1-8) infusions of iron, which consisted of sodium ferric gluconate (n = 11), iron dextran (n = 4), or iron sucrose (n = 1). Fourteen of 16 patients showed an increase in hematocrit values after parenteral iron supplementation. The median hematocrit value for these patients rose from 28.75% to 32.75% ($P < .0001$), the mean corpuscular volume (MCV) rose from 84.7 to 89.9 ($P = .006$), and the TSAT level rose from 8.1% to 21.2% ($P < .0001$). Among the 14 patients who showed improvement in hematocrit values after parenteral administration of iron, 8 had previously received oral therapy with iron without improvement in their hematocrit values, and their disease was deemed refractory to oral iron therapy.

Discussion

Anemia is the foremost cause for initiation of therapy in patients with WM, yet for many patients the extent of anemia is discordant with the level of bone marrow disease involvement. In a series of 356 newly diagnosed patients with WM, no correlation between bone marrow disease involvement and hematocrit levels was observed.[1] The recent identification of hepcidin production by WM lymphoplasmacytic cells and the presence of elevated hepcidin levels in patients with WM prompted us to examine iron deficiency as a possible contributor to anemia in patients with WM.[6] The contribution of hepcidin to iron deficiency, as well as to anemia in other B-cell lymphoproliferative disorders, has also been recognized.[14-16] Given these findings, we undertook a practice improvement initiative as part of an ABIM practice improvement project wherein untreated patients with WM who presented with anemia would have their TSAT levels determined at baseline. The findings of this study showed that half of patients with WM were iron deficient as defined

by a TSAT level of ≤ 20%, whereas a quarter of patients with WM had severe iron deficiency defined by a TSAT level of ≤ 10%.

An important recognition in these studies was the potential benefit of parenteral iron infusions for improving anemia in patients with WM and severe iron deficiency, including for patients in whom a previous trial of oral iron supplementation had failed. The recognition that parenteral iron supplementation may offer an advantage over oral iron supplementation in patients with cancer-related anemia has been previously recognized with an erythrocyte-stimulating agent (ESA).[17,18] Improvements in anemia after parenteral iron vs. no iron administration in association with an ESA in lymphoproliferative disorders has also been reported.[19] However, in our patient population, parenteral iron was administered without an ESA, and our observations were limited to untreated patients. These observations may therefore serve as a catalyst for further clinical trial investigation of parenteral iron supplementation as an alternative to an ESA, in conjunction with an ESA, or in combination with chemotherapy in patients with WM who present with anemia. It remains possible that a trial of parenteral iron may be attempted before the use of chemotherapy in select candidates with low tumor burden who meet the criteria for treatment based on consensus guidelines[12] and who, except for mild to moderate anemia, are otherwise asymptomatic. The optimal agent for parenteral iron administration—and the dose, schedule, and duration of treatment—remain to be clarified, as does the duration of potential benefit before repeated treatment or implementation of chemotherapy becomes necessary. Prospective clinical trials will be required to clarify these important issues.

In conclusion, routine screening of TSAT levels may help identify patients with WM and severe iron deficiency. Use of parenteral iron is associated with improved hematocrit values, MCV, and TSAT levels in patients with WM who present with severe iron deficiency, including patients whose disease was refractory to previous oral iron supplementation.

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Disclosure

The authors have stated that they have no conflicts of interest.

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