peripheral blood γ-globin to β-globin messenger RNA was 0.89 (range, 0.34-1.4).

Vorinostat was well tolerated at the doses tested. Vorinostat toxicity (fatigue, abdominal pain) was mild to moderate, with the exception of pain, indistinguishable from sickle pain in 3 patients and headaches in 1 patient. With intermittent dosing, we were able to prevent thrombocytopenia, a common effect of vorinostat use in malignancy. However, it is unclear whether sufficient doses were used in this study because neither thrombocytopenia nor a convincing induction of HbF was produced.

We have demonstrated the safety and tolerability of an oral pan-HDAC inhibitor, vorinostat, in 5 patients with SCD, with minimal adverse events. Future studies with vorinostat should employ higher cumulative weekly doses, probably marked by induction of relative thrombocytopenia. Potentially more promising is the potential of using HDAC1 and HDAC2 selective agents that would mediate HbF induction[6] (with tolerability that allows more robust dosing) and using combinations of HDAC inhibitors with hydroxyurea.

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To the editor:

Serum hepcidin levels predict response to intravenous iron and darbepoetin in chemotherapy-associated anemia

Patients undergoing chemotherapy for cancer frequently experience anemia, which may require red blood cell (RBC) transfusions.[1] The erythropoiesis-stimulating agents (ESAs) epoetin and darbepoetin reduce transfusion needs and increase hemoglobin levels in 40% to 70% of patients with chemotherapy-associated anemia (CAA) and are approved by the Food and Drug Administration for CAA.[2]

In renal anemia, iron deficiency is the most common cause of suboptimal ESA response, and iron deficiency may also contribute to ESA nonresponse in other subsets of patients.[3,4] Even patients with normal or elevated total-body iron stores may have diminished iron available to developing erythroid cells ("functional iron deficiency") as a result of tumor-associated inflammation and macrophage sequestration of iron.[5] IV iron may provide bioavailable iron and augment response to ESA therapy in both functional and total iron deficiency states.[6]

At least 11 prospective trials have shown benefit from IV iron in combination with an ESA for patients with CAA, but one study did not show benefit.[7] The sole trial that failed to reach its primary end point—the largest IV iron trial in CAA conducted to date—was a randomized multicenter study (MC04CC, clinicaltrials.gov #NCT00661999) of

Table 1. Comparison of hemoglobin and transfusion end points by serum hepcidin subgroup and treatment assignment

	DA + placebo	DA + oral iron	DA + IV iron (pts receiving <4 doses IV iron)	DA + IV iron (pts receiving 4 or 5 doses IV iron)	P for comparison of 4 or 5 dose IV iron group with non-IV iron groups	P for comparison of 4 or 5 dose IV iron group with all other groups	P for comparison of any IV iron (including <4 doses) with non-IV iron groups
Proportion of patients who achieved a protocol-defined hemoglobin response							
Total	106/163 (65%)	109/163 (67%)	40/71 (56%)	74/92 (80%)	.0079	.0028	.23
Hepcidin 1st tertile (≤20.2 ng/mL)	30/47 (64%)	26/41 (63%)	12/20 (60%)	24/26 (92%)	.0050	.0038	.083
Hepcidin 2nd tertile (>20.2-64.3 ng/mL)	36/53 (68%)	32/53 (60%)	6/11 (55%)	20/21 (95%)	.0048	.0018	.069
Hepcidin 3rd tertile (>64.3 ng/mL)	23/36 (64%)	29/37 (78%)	14/24 (58%)	25/36 (69%)	.99	.88	.44
Hepcidin missing	17/27 (63%)	22/32 (69%)	8/16 (50%)	5/9 (56%)	.68	.54	.22
Proportion of patients who required RBC transfusion							
Total	22/163 (13%)	21/163 (13%)	12/71 (17%)	8/92 (9%)	.25	.12	.79
Hepcidin 1st tertile	6/47 (13%)	4/41 (10%)	2/20 (10%)	0/26 (0%)	.072	.073	.18
Hepcidin 2nd tertile	8/53 (15%)	9/53 (17%)	2/11 (18%)	0/21 (0%)	.049	.047	.16
Hepcidin 3rd tertile	6/36 (17%)	5/37 (14%)	4/24 (17%)	6/35 (17%)	.78	.82	.77
Hepcidin missing	2/27 (7%)	3/32 (9%)	4/16 (25%)	2/9 (22%)	.21	.39	.054

Comparison of hemoglobin response and RBC transfusion needs in the MC04CC trial, stratified by serum hepcidin level. MC04CC trial eligibility included hemoglobin <11.0 g/dL, serum ferritin >20 ng/mL, and transferrin saturation <60%.[8] Median transferrin saturation of enrolled patients was 18.5% and median ferritin was 324 ng/mL. The study's primary end point was a hemoglobin increment of ≥2.0 g/dL in the absence of transfusions or achievement of hemoglobin of ≥12.0 g/dL; transfusion avoidance was a secondary end point. There was no overall erythropoietic benefit from parenteral iron compared with oral iron or placebo. All P values are for 2-sided χ^2 test, comparing within tertile/row.

DA, darbepoetin alfa; pts, patients; RBC, red blood cells.

darbepoetin alfa (DA) combined with either IV ferric gluconate, oral ferrous sulfate, or no iron supplementation in 502 patients with CAA.[8] In MC04CC, ferric gluconate was administered at a dose of 187.5 mg every 3 weeks (5 total doses, 937.5 mg cumulative iron dose).

The peptide hepcidin regulates systemic iron homeostasis and might serve as a biomarker for patients more likely to benefit from IV iron.[9] In iron-deficient states, serum hepcidin levels are usually low, whereas in iron overload or inflammation, hepcidin levels are high, decreasing bioavailable iron and sequestering iron in macrophages and hepatocytes. High serum hepcidin levels can make oral iron ineffective by decreasing gut iron absorption.

The relationship between hepcidin and response to ESAs and oral or IV iron therapy has not been systematically studied in patients with CAA. To better understand relationships between hepcidin and treatment outcomes in CAA and gain additional insight into MC04CC trial results, hepcidin levels were assessed in MC04CC-enrolled patients in a preplanned analysis.

Serum hepcidin concentration was measured in pretreatment samples from 405 (83%) of 489 eligible patients using a quantitative mass spectrometry–based method described elsewhere.[10] Hepcidin was analyzed both as a continuous variable and divided into tertiles, and hepcidin levels were compared with hemoglobin and transfusion responses, patient characteristics including other iron parameters (eg, ferritin, transferrin saturation), and treatment-emergent adverse events. Descriptive statistics were used to compare hepcidin levels in responding vs nonresponding patients. All tests were 2-sided, with type I error rates of .05. SAS software (version 9; SAS Institute, Cary, NC) was used for analyses.

Study participants with serum hepcidin levels in the lower two tertiles experienced a better clinical response to DA plus higher doses of IV iron than patients with lower hepcidin levels who did not receive higher-dose IV iron (Table 1). The 47 patients who received 4 or 5 doses of IV iron and had lower serum hepcidin levels did not require any RBC transfusions, compared with the 14% transfusion rate for the remaining study population (P = .0065), a transfusion rate comparable with other IV iron studies. Among patients

with higher serum hepcidin, IV iron offered no benefit compared with oral iron or placebo. These relationships persisted when hepcidin was analyzed as a continuous variable. No correlation was observed between hepcidin and serum ferritin, transferrin saturation, or adverse events. Pretreatment C-reactive protein, which was also assessed during this study, did not predict response to therapy.

Low serum hepcidin levels may characterize iron-deficient patients more likely to benefit from intensive iron supplementation.[11] Higher hepcidin levels would be expected in patients with extensive tumor-associated inflammation, and the failure of IV iron to augment erythropoiesis in this subgroup casts doubts on whether IV iron alone can routinely overcome functional iron deficiency in patients with anemia of inflammation. However, the influence of hepcidin on response to ESA therapy is likely complex, involving factors other than iron. For instance, hepcidin biosynthesis in the liver is downregulated by expansion of erythropoiesis and may also be directly modulated by erythropoietin, and therefore may change during ESA treatment.[12,13] In the future, modulation of hepcidin levels via an antihepcidin l-oligoribonucleotide or other strategies may improve treatment of inflammation-associated anemia.[14]

ESAs are costly, and serious concerns about ESA safety in CAA have emerged in the last decade. Maximizing hemoglobin response while minimizing administered ESA dose is an attractive goal of IV iron. Serum hepcidin measurement may help predict the response to ESAs and supplemental iron. Analysis of hepcidin levels in other CAA data sets will be informative.

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