Thrombocytosis and venous thromboembolism in cancer patients with chemotherapy induced anemia may be related to ESA induced iron restricted erythropoiesis and reversed by administration of IV iron

David H. Henry,[1]* Naomi V. Dahl,[2] and Michael A. Auerbach[3]

ESA therapy can increase hemoglobin, decrease blood transfusions, and improve quality of life in patients with chemotherapy induced anemia (CIA). Despite its benefits, ESA therapy increases the risk of venous thromboembolism (VTE) in cancer patients by 50% and can also cause iron restricted erythropoiesis in CIA patients, which may augment the tendency to develop VTE. We postulated that thrombocytosis, a risk factor for VTE in cancer patients, in CIA patients on ESA therapy might be a result of ESA induced iron restricted erythropoiesis. We performed a retrospective analysis of 187 CIA patients who were randomized to receive weekly Epoetin and IV ferric gluconate, oral ferrous sulfate, or no iron for 8 weeks. Nineteen patients experienced 29 VTEs, and patients, whose platelets increased to ≥350,000 cells/uL were three times more likely to experience a VTE (OR 2.9, $P = 0.036$, logistic regression) with a four times greater incidence of VTE (IRR 4.4, $P = 0.001$, Poisson regression). Patients treated with IV iron were significantly less likely to develop platelets of ≥350,000 cells/uL (IRR 0.7, $P = 0.013$, Poisson regression) and had a decreased incidence of VTE. Our study suggests that ESA associated VTE in CIA patients may be, in part, related to the thrombocytosis of ESA induced iron restricted erythropoiesis and may be countered by IV iron.

Anemia is common in cancer patients [1–3]. Patients may present with or develop anemia during chemotherapy treatment [1–3]. The mechanism of chemotherapy-induced anemia (CIA) is partly a consequence of anemia of chronic disease and chemotherapy induced myelosuppression [1,4,5]. Anemia of chronic disease is characterized by a combination of poor iron mobilization, decrease in red cell survival, and inadequate levels of erythropoietin (EPO) relative to the degree of anemia [4,5]. Erythropoietic stimulating agents (ESA) were studied in CIA patients and approved for use in the United States in 1993 (Epoetin Alfa, Procrit®™) and in 2002 (Darbepoetin Alfa, Aranesp®™). After nearly 20 years of placebo-controlled clinical-trials of ESAs in CIA patients, the data suggest that, when used on label, ESAs are safe [6–8]. The initial FDA label allowed treatment with an ESA when hemoglobin was 12 g/dl or less; but safety issues in several ESA studies led to the following label changes: in CIA patients, initiate ESA when hemoglobin is <10 g/dl and use the lowest dose possible to avoid red blood cell transfusion [9]. In addition, treating CIA in curable cancer patients is neither indicated nor contraindicated. Meta-analyses of ESAs in CIA agree on the increased risk of venous thromboembolism (VTE) with ESA use compared with placebo or standard of care [7,8,10,12]. The mechanism for this increase in VTE is unknown, but it has been postulated that ESAs may affect vascular endothelial cells either directly or indirectly via generation of inflammatory cytokines [11]. Most of these meta-analyses of ESA in CIA show no increase in mortality compared with placebo or standard of care [7,8,10]. However, 8 out of 60 placebo controlled trials of ESA in cancer patients in one meta-analysis, and two other meta-analyses did show a greater mortality in the ESA-treated patients [6,8,12]. The mechanism for the higher mortality in these trials remains unclear. If this negative survival effect is a consequence of increased VTE, is it a direct result of higher ESA doses, higher targeted hemoglobin concentrations, or possibly thrombocytosis as a consequence of ESA induced iron restricted erythropoiesis?

ESA treatment increases hemoglobin level by drawing on iron stores, which are needed for efficient iron dependent erythropoiesis. An absolute or relative iron deficiency may result, leading to iron restricted erythropoiesis and, consequently, a suboptimal response to ESAs [13]. Absolute iron deficiency is associated with thrombocytosis. Although uncommon without other risk factors, an increase in cardiovascular events has been reported in iron deficient patients with thrombocytosis [14]. In one study, it was shown that higher platelet counts in oncology patients were associated with an increased rate of thromboembolic events (adjusted OR for platelet count ≥ 350,000/μL vs. < 200,000/μL was 2.81, $P = 0.0002$) [15].

Approximately 20% of cancer patients will experience a VTE during their course of therapy. A recent study of ambulatory cancer patients on chemotherapy attempted to develop a model to predict which patients are at the greatest risk for VTE and found a pretreatment platelet count of ≥350,000 cells/μL was predictive [15]. Whereas absolute iron deficiency is associated with reactive thrombocytosis, we postulated that iron-restricted erythropoiesis as a result of ESAs in anemic cancer patients may contribute to increased platelet counts [16]. Therefore, we hypothesized that elevated platelet counts could be one of the factors contributing to the increased incidence of VTE in cancer patients on ESA therapy, and that this feature might be abrogated by IV iron administration [17]. We conducted a post-hoc analysis of data presented on the safety and efficacy of intravenous iron in anemic cancer patients receiving chemotherapy and Epoetin Alfa to test this hypothesis [18].

Characteristics of the study participants are shown in Supplementary Table I. There were no significant differences between groups in baseline parameters, with the exception of gender. Nor were there any differences in chemotherapy intensity or myelosuppression among the treatment groups, with no significant differences in proportion of patients receiving platinum-based chemotherapy, or in mean area under neutrophil curve (all $P > 0.9$). During the course of the study, there were no significant differences in transfusion requirements or in average weekly epoetin dose among treatment groups. Iron-restricted erythropoiesis was more prevalent in the no iron and oral iron arms as demonstrated by transferrin saturation (TSAT), reticulocyte hemoglobin content (CHr), and percent hypochromic red cells (Fig. 1).

Nineteen of the 187 patients who participated in this study experienced 29 thromboembolic events (Supplementary Table II). Seven patients in the oral iron group experienced 11 events, 6 patients in the no-iron group experienced 11 events, and 6 patients in the IV iron group experienced 7 events, (Characteristics of patients who experienced VTE vs. those who did not are available in Supplementary Table III). Patients whose platelet counts increased to values ≥350,000 cells/μL during the study were approximately three times more likely to experience VTE than other patients (OR 2.8, $P = 0.036$, logistic regression). This was independent of the effects of platinum-based chemotherapy (OR for platinum 3.42; $P = 0.028$), gender and baseline platelet count (both $P > 0.6$).

The incidence rate of thromboembolic events was fourfold greater among patients whose platelet counts increased from baseline to values ≥350,000 cells/μL at any time during the study (IRR 4.4, 95% CI 1.9–10.2, $P = 0.001$, Poisson regression). This too was independent of the effects of platinum-based chemotherapy. In a multivariate model, controlling for platinum-based chemotherapy, the IRR for thromboembolic events among patients whose platelet counts increased to ≥350,000 cells/μL was 4.1 (95% CI 1.8–9.7), while the IRR for thromboembolic events among patients receiving platinum based chemotherapy was 4.4 (95% CI 1.8–10.9), both $P = 0.001$. Neither incidence of post-baseline increase in platelets alone, nor incidence of platelet count ≥350,000 cells/μL alone was associated with a significantly increased incidence of thromboembolic events (both $P > 0.7$).

Among patients who experienced VTE, the mean baseline platelet count was 324, 000 cells/μL, increasing to a mean peak of 406, 000 cells/μL at a median of 3 weeks from start of therapy. The peak platelet count coincided with a mean change from baseline in CHr of −1.1 pg.

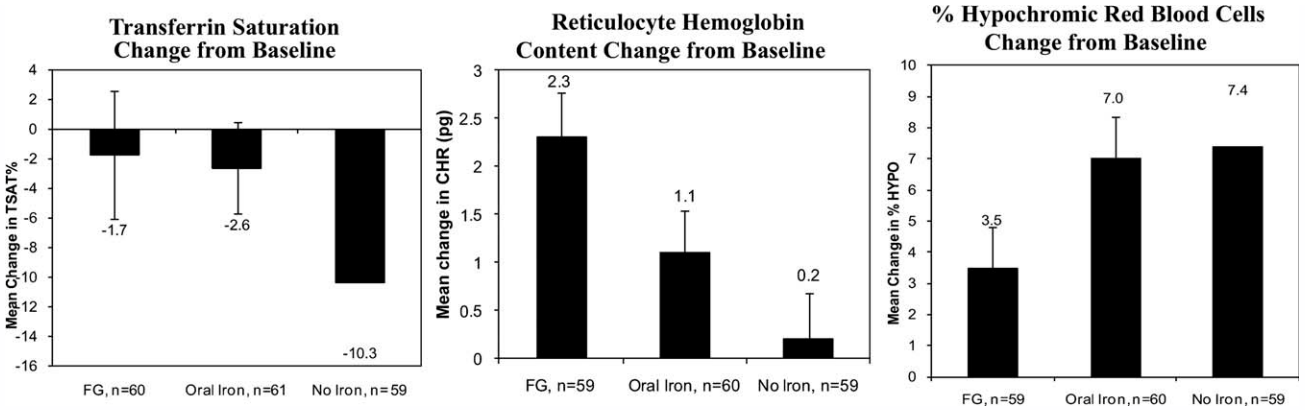

Figure 1. Changes from baseline to last observation in iron parameters with Epoetin Alfa and no iron, oral iron, or IV iron (FG=ferric gluconate weekly x 8 weeks, oral iron = ferrous sulfate 325mg orally TID x 8 weeks). Note that the transferrin saturation and the percent hypochromic RBCs both migrate toward iron restricted erythropoiesis in all groups, but least so in the IV iron group.

Those treated with IV iron were significantly less likely to experience a post-baseline platelet count ≥350,000 cells/uL than those with ESA treatment alone (IRR 0.7, $P = 0.013$, Poisson regression) (Figs. 2 and 3). Treatment with IV iron was associated with a statistically nonsignificant 40% reduction in the rate of thromboembolic events (IRR 0.6, $P = 0.2$). However, if an increased platelet count was adjusted for, then IV iron treatment was not an independent predictor of VTE, implying that the decrement observed was likely mediated through its effect on platelet count.

While the debate around the safety, efficacy, and expense of ESAs in CIA patients continues, the preponderance of the evidence suggests that ESAs decrease the number of necessary transfusions, increase hemoglobin, and improve quality of life parameters in responders. Only two out of three CIA patients respond to ESA therapy, so improving hemoglobin response rates and the efficiency of ESAs is imperative. Nine of ten controlled studies comparing ESA plus IV iron to ESA alone have demonstrated that IV iron improves response rates to ESAs, even in patients who are iron replete [19,20]. The one trial that failed to show a difference when IV iron was added to ESAs in CIA patients delivered IV iron at a dose and rate that were considerably lower when compared with all other IV iron trials [21]. A subsequent analysis of this same data set revealed that those patients who actually received greater than half of the IV iron per protocol had a significantly better response than those who did not [22]. Thus, it could be possible that IV iron supplements the iron stores, which are not as readily available for erythropoiesis and thereby overcomes iron restricted erythropoiesis. This suggests that ESA administration can cause iron-restricted erythropoiesis in most patients, even those with adequate iron stores.

One of the principal safety concerns of ESAs in CIA is the increased risk of VTE, with an approximate 1.5 hazard ratio for ESA treated patients [23]. The platelet count rises in absolute iron deficiency. This rise also occurs in iron replete CIA patients who experience iron-restricted erythropoiesis during ESA therapy. A retrospective review of our ESA plus IV iron study suggests that those whose post baseline platelet counts rose above 350,000 cells/uL were more likely to experience a VTE event. In those receiving intravenous iron, whose iron availability would be the greatest, the incidence of VTE appeared lower compared with those receiving oral or no iron. This IV iron—platelet lowering effect has been seen in non hemodialysis chronic kidney disease (CKD) patients receiving IV iron. In a study of CKD patients receiving monthly DA, IV iron patients had significantly lower platelet counts, with the greatest reduction in platelet count in those who received a total of 1000 mg IV iron compared with those who received a total of 500 mg IV iron [24]. Similar results were observed in the **D**ialysis Patients **R**esponse to **IV** Iron with **E**levated Ferritin (DRIVE) study, in which Patients with hemoglobin <11 g/dl, ferritin 500 to 1,200 ng/ml, TSAT <25%, and epoetin dosage >225 IU/kg per week or >22,500 IU/week received a 25% increase in epoetin dose, and were randomized to receive 1 g of IV iron or no iron. At 6 weeks, hemoglobin increased more in the IV iron group than the control group [25]. However, the control group patients developed progressive iron-restricted erythropoiesis. By the end of the study, their reticulocyte hemoglobin content (CHr) fell while remaining unchanged in the IV iron group (mean change −0.9 pg vs. 0.0 pg; $P = 0.002$). Platelet count in patients receiving IV iron decreased while remaining unchanged in patients not given iron (mean change −29,000/μL vs. −0/μL; $P = 0.017$) [17].

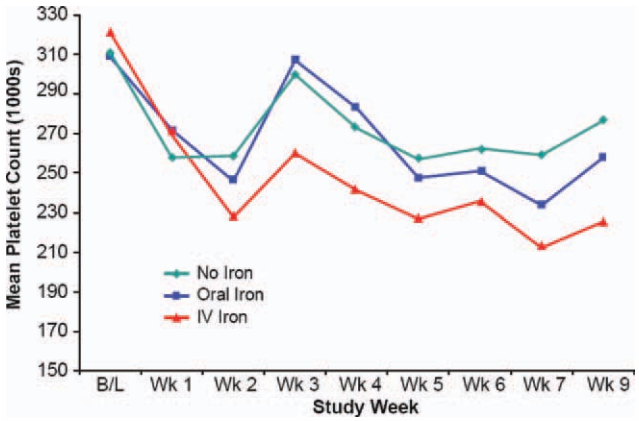

Figure 2. Platelet Count by Weekly Study Visit. The lowest platelet counts are observed in the IV iron arm. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

A risk model for VTE in cancer patients noted an increased risk of VTE when platelet counts were greater than 350,000 cells/μL prior to initiation of chemotherapy [26]. If 20% of cancer patients develop VTE and ESA use in CIA increases this risk, strategies to better understand and reduce this risk are in order. If our observation is replicated by other studies, it could lead to a better understanding of the mechanism of increased VTE in patients treated with ESAs. In particular, we encourage a retrospective review of other ESA clinical trials to see if this hypothesis can be confirmed, especially in other intravenous iron trials similar to ours. In addition, we encourage prospective trials to examine this particular issue to see if ESA use and platelet count elevation are associated with a higher incidence of VTE in CIA patients, who are already at increased risk, and whether or not intravenous iron can decrease the incidence of VTE while optimizing the response to ESAs.

Methods

This was a post-hoc analysis of data from our previously published open label, randomized, controlled, multicenter, prospective trial [18]. Inclusion criteria included: patients ≥18 years, ECOG performance status of 0, 1, or 2, life expectancy of at least 24 weeks, diagnosis of nonmyeloid malignancy, hemoglobin level <11 g/dl, serum ferritin ≥ 100 ng/ml, and/or TSAT > 15% (to exclude patients with absolute iron deficiency), and within 1 week of initiation of a chemotherapy. Exclusion criteria included: serum ferritin >900 ng/ml and/or TSAT >35%, serum creatinine >2.0 mg/dl, Epoetin Alfa or IV iron therapy within 30 days of enrollment or oral iron therapy within 7 days of enrollment.

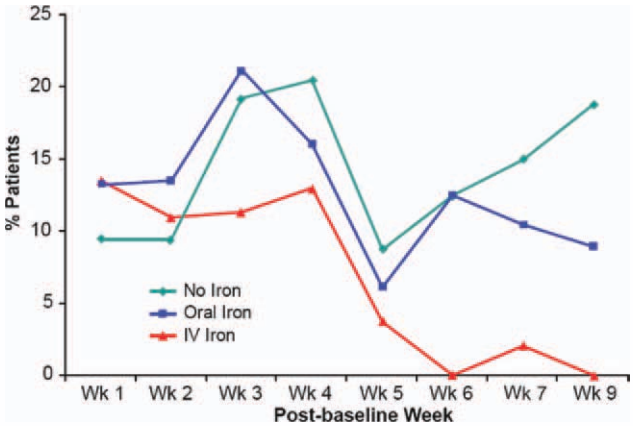

Figure 3. Percent of Patients in each arm whose platelet counts increased from baseline to a value $\geq$ 350,000 cells μl per Weekly Study Visit. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

All patients received Epoetin Alfa 40,000 units subcutaneously weekly, increasing to 60,000 units per week if insufficient response occurred after 5 weeks. Patients were randomized on a 1:1:1 basis to receive either no iron, oral iron (325 mg of ferrous sulfate orally three times daily), or 125 mg IV ferric gluconate (Ferrlecit®, then Watson, Morristown, NJ, now Sanofi-Aventis, Paris, France) intravenously weekly for a total of eight weeks.

The population for this post-hoc analysis included all patients who were exposed to study drug (Oral iron and IV Iron groups) or who completed the baseline clinic visit (No Iron group). Adverse events were coded using Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) terminology. To compare the differences between groups in the likelihood of a patient experiencing a thromboembolic adverse event, odds ratios (OR) were analyzed with logistic regression. To compare the differences between groups in the rate of occurrence of thromboembolic adverse events (events/patient-weeks), incident rate ratios (IRR) were analyzed with Poisson regression.

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[1]Department of Medicine, Pennsylvania Hospital, University of Pennsylvania, Philadelphia, Pennsylvania; [2]Watson Laboratories, Inc., Parsippany, New Jersey; [3]Auerbach Hematology and Oncology; Department of Medicine, Georgetown University, Baltimore, Maryland
**Correspondence to: David H. Henry, M.D., Joan Karnell Cancer Center, Pennsylvania Hospital, 230 West Washington Square, Philadelphia, PA 19106, USA*
E-mail: davidhenry@pennoncology.com
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