Preoperative Intravenous Iron and Erythropoietin to Treat Severe Anemia in Patient With Stage 4 Kidney Disease Before Oncologic Surgery: A Case Report

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Preoperative treatment of anemia with intravenous iron is inconsistent despite known risks of anemia and allogeneic blood transfusions. Limited research exists on the effectiveness of preoperative intravenous iron for chronic kidney disease (CKD) patients. We discuss a patient with severe anemia from advanced CKD, endometrial cancer, and menometrorrhagia. Her hemoglobin increased more than 2 g/dL after erythropoietin and two 750-mg ferric carboxymaltose infusions 5 weeks before a total abdominal hysterectomy and avoided blood transfusions perioperatively. By raising hemoglobin, preoperative intravenous iron and erythropoietin reduce blood transfusions and consequent risk of future allograft rejection and alloimmunization in potential transplant recipients. (A&A Practice. 2020;14:e01234.)

GLOSSARY

CKD = chronic kidney disease; **EPO** = erythropoietin; **EQUATOR** = Enhancing the Quality and Transparency of Health Research; **Hg** = hemoglobin; **HIPAA** = Health Insurance Portability and Accountability Act; **HLA** = human leukocyte antigen; **IDA** = iron deficiency anemia; **IV** = intravenous

We present the case of a patient with severe anemia from advanced chronic kidney disease (CKD) and chronic blood loss from endometrial cancer treated with intravenous (IV) iron and erythropoietin in the preoperative clinic before a hysterectomy. Preoperative anemia increases the risk of perioperative complications and mortality. Perioperative allogeneic blood transfusions are strongly associated with adverse events, including increased mortality, postoperative pneumonia, and prolonged hospital length of stay.¹ In patients with CKD, perioperative allogeneic blood transfusions and consequent human leukocyte antigen (HLA) sensitization can negatively impact the probability of finding an organ match. Additionally, it has been reported that multiple pretransplant allogeneic blood transfusions (>5 units) are associated with graft failure in recipients.²

Numerous studies demonstrate that preoperative IV iron infusions for patients with iron deficiency anemia (IDA) can result in a robust increase in hemoglobin (Hg) and can eliminate the need for perioperative allogeneic blood transfusions.³ However, the application of iron infusions preoperatively in patients with anemia has been inconsistent across hospitals and countries due to concerns regarding safety and efficacy despite evidence that has shown otherwise.⁴ Furthermore, limited research exists on

the effectiveness of preoperative IV iron infusions for CKD patients with anemia undergoing surgery. Due to elevated levels of hepcidin and blood loss from frequent dialysis and blood draws, more than half of patients with advanced CKD are estimated to have IDA.⁵

In practice, there may be concerns surrounding the robustness in Hg increase within the short time period between the preoperative visit and surgery especially in patients with CKD and cancer due to erythropoietin deficiency and bone marrow suppression. We discuss a case where a patient with stage 4 CKD, severe anemia, endometrial cancer, and vaginal bleeding benefitted from preoperative IV iron and erythropoietin treatment. The patient subsequently avoided perioperative blood transfusions.

The patient provided Health Insurance Portability and Accountability Act (HIPAA) authorization and written consent to publish this case report. This article adheres to the applicable Enhancing the Quality and Transparency of Health Research (EQUATOR) guidelines.

CASE DESCRIPTION

Our patient is a 47-year-old woman with a history of stage 4 CKD due to tubular interstitial disease secondary to lithium use for schizophrenia. She presented to the preoperative clinic at our institution before robotic-assisted hysterectomy and bilateral salpingo-oophorectomy for adenocarcinoma of the endometrium. Before the cancer diagnosis, the patient was being evaluated for kidney transplantation. Her medical history was significant for diabetes mellitus type 2, hypertension, hypothyroidism, schizophrenia, and acute or chronic IDA.

The etiology of her anemia is multifactorial, including menometrorrhagia, erythropoietin deficiency, and chronic inflammation from cancer and CKD. In the previous 11 months, she had received 4 ferumoxytol infusions (510 mg

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each) and 2 units of allogeneic packed red blood cells. After the insertion of an intrauterine device, her heavy bleeding markedly improved, but she continued to have monthly periods. Surgery was planned as definitive treatment for menometrorrhagia and endometrial adenocarcinoma.

This patient presented to our preoperative clinic with a Hg of 7.5 g/dL, iron of 37 µg/dL, transferrin of 221 mg/dL, transferrin saturation of 13%, and ferritin of 21.4 ng/mL. The patient reported fatigue and an intolerance to cold temperature despite normal thyroid hormone concentrations. We recommended postponing surgery until her Hg was above 9.0 g/dL. The patient received 1 erythropoietin injection and 2 ferric carboxymaltose infusions (750 mg each) 1 week apart with notable increases in Hg and reticulocyte responses within 5 weeks of her surgery (Figure). Due to an oversight, she only received the first of 2 erythropoietin injections. Had she received the second erythropoietin, her Hg response may have been more robust. One week after the first treatment of ferric carboxymaltose and erythropoietin, her reticulocyte count was 5% (normal is <1%), and just 15 days after the first treatment, her Hg was 9.2 g/dL with a reticulocyte count of 1.8%. After these results, the preoperative clinic communicated to the surgeons that surgery could be scheduled at any time. However, due to nonmedical issues, surgery was not scheduled until almost 3 weeks later. Three days before surgery (and 32 days since her first iron and erythropoietin), her Hg was 9.7 g/dL with a reticulocyte count of 1.0%. The patient had an uneventful surgery under general endotracheal anesthesia and hemodynamics were monitored with an arterial line. There was minimal blood loss during surgery and the patient's postoperative Hg was 9.1 g/dL.

In summary, by delaying surgery only 15 days, this patient's Hg increased by more than 2 g/dL in spite of stage 4 CKD, endometrial cancer, and ongoing blood loss. We avoided allogeneic blood transfusions by giving ferric carboxymaltose and erythropoietin. By limiting the number of lifetime transfusions, her chances of having a successful kidney transplantation may be improved.

DISCUSSION

Preoperative anemia and CKD are independent risk factors for adverse events and perioperative allogeneic blood

transfusions in various surgeries, including orthopedic and cardiac procedures.^{6,7} Among CKD patients specifically, preoperative anemia is an independent risk factor for perioperative allogeneic blood transfusions. In 1 study, patients with CKD had higher rates (50% vs 28.5%) of perioperative transfusions compared to non-CKD patients.⁸ In another study, patients with CKD who had lower preoperative Hg had increased odds (0.74) of perioperative transfusions.⁹ Our patient therefore had a very high risk of perioperative transfusions given that she had both advanced CKD and severe anemia.

Allogeneic blood transfusions for patients with CKD potentially result in the development of HLA antibodies that limit kidney donor matches or increase the risk of allograft rejection if successfully transplanted.² Numerous studies show the effectiveness of IV iron infusions in patients with anemia.^{3,10} However, few studies examine the response to iron infusions in patients with advanced CKD before a major surgery. Our case demonstrates that IV iron and erythropoietin can successfully increase the Hg of a patient with severe anemia and advanced CKD before a major surgery with expected blood loss, and eliminate the need for allogeneic blood transfusions.

Compared to oral iron, there is no demonstrable increase in adverse events with IV iron such as infections or hypersensitivity reactions with the newer formulations.⁴ Non-dialysis-dependent CKD patients had a greater increase in Hg of >1 g/dL after IV iron compared to oral iron, while the rate of adverse events was similar.⁴ Efficient testing protocols to identify patients who can benefit from IV iron preoperatively in 1 clinic visit have been described.¹¹ Despite its safety and efficacy, recommendations on when to give iron infusions vary. Currently, the American Society of Anesthesiologists Task Force recommends preoperative erythropoietin with or without iron to reduce intraoperative allogeneic blood transfusions and the administration of iron to patients with IDA only if time permits.¹² On the other hand, the European Society of Anesthesiology recommends assessing for anemia 4–8 weeks before surgery and treating IDA with oral or IV iron supplementation.¹³

The practice of giving iron infusions is heterogeneous across hospitals and countries. A survey of European hospitals showed varied practices, with only 2 nations having

Figure. Timeline of IV iron infusion, EPO, and Hg and reticulocyte responses. EPO indicates erythropoietin; Hg, hemoglobin; IV, intravenous.

national guidelines.¹⁴ In 1 hospital, patients in all departments except for gynecology and orthopedics were screened for preoperative anemia.¹⁴ Only 67.4% of centers in the United Kingdom that offered perioperative anemia screening had access to IV iron therapy.¹⁵ In this study, practitioners surveyed commented that the ability to provide IV iron was restricted to certain cancers (urological and colorectal), or was limited by lack of an anemia management pathway and by proximity to the date of surgery. Providers may be hesitant to delay surgery to give IV iron, but a recent randomized controlled trial by Spahn et al³ demonstrated that giving ferric carboxymaltose, erythropoietin, folic acid, and vitamin B₁₂ just 1 day before surgery reduced the number of allogeneic blood transfusions. Despite newer and safer formulations of IV iron, due to variable knowledge of IV iron and inconsistent anemia management pathways, preoperative anemia may be undertreated or treated using other less effective or hazardous methods such as oral iron or allogeneic blood transfusions.^{4,15}

Our case demonstrates that even with chronic inflammation and potential bone marrow suppression from both advanced CKD and cancer and ongoing blood loss, our patient nevertheless had a robust response in Hg with an increase in over 2 g/dL within a few weeks after 1 erythropoietin and 2 IV iron infusions. We chose a conservative target for a CKD patient of a Hg of 9 g/dL to not delay surgery more than was necessary, because the surgeons anticipated a low risk of major blood loss.⁵ Our patient's age, chronic anemia, and lack of cardiovascular disease suggested this was acceptable. Blood transfusions appear to result in immunomodulation that may lead to an increase in cancer progression.¹⁶ There is evidence both supporting worse outcomes in patients receiving autologous blood, and other studies showing no risk of cancer progression.¹⁶ In this case, the benefit of treating anemia without blood transfusion extends beyond the immediate surgery. Given the potential for future allograft rejection or HLA sensitization in potential transplant recipients after multiple blood transfusions, IV iron and erythropoietin benefit surgical patients being considered for organ transplantation. ■■

DISCLOSURES

Name: Betty M. Luan-Erfe, MD.

Contribution: This author helped care for the patient, gather and analyze the data, and draft the case report.

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Contribution: This author helped care for the patient, edit the case report, and facilitate communication with the patient.

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