IRON CORNER

Management of Iron Deficiency Anemia in Chronic Kidney Disease

Summary

- Anemia is common in CKD and may be managed with iron alone or in conjunction with ESA.
- Left untreated, anemia has adverse effects on cardiac function, QOL, CKD progression and survival.

Introduction

CKD is a progressive disease that gradually impairs kidney function, usually over a period of years. According to the National Kidney Foundation (NKF), approximately 8 million people in the US are living with moderate (stage 3) or severe (stage 4) CKD and are not yet receiving dialysis.[1,3] CKD often progresses to end stage renal disease (ESRD), where the kidneys fail and renal replacement therapy such as dialysis or transplantation is required to sustain life. The primary goal of treatment for CKD is to slow the progression of the disease, mainly by controlling the underlying common causes: hypertension and/or diabetes. Patients with CKD suffer from a myriad of complications, which may also affect CKD progression. These include malnutrition, bone disease and anemia, usually accompanied by iron deficiency.

Causes

Iron deficiency and anemia, often multifactorial in its etiology, are significant complications of CKD and ESRD, developing early in the course of the disease and progressing with loss of renal function.[2] Published data indicate that approximately 44% of patients with CKD stage 3 or 4 are anemic (defined as Hb <13.5 g/dL for men and Hb <12.0 g/dL for women), and the prevalence of anemia increases to 75% in patients reaching CKD stage 5 (ESRD).[1] The cause of this anemia is, as mentioned, multi-factorial, and includes the inability of the failing kidney to produce enough erythropoietin to stimulate adequate hematopoiesis, iron deficiency, and shortened red blood cell survival. Iron deficiency is a common and often predominant cause of anemia in CKD patients. Iron deficiency and iron deficiency anemia can be due to both poor nutrition and blood loss and can be exacerbated by use of erythropoietic stimulating agents (ESAs). ESA therapy depletes iron stores as iron needs are increased to produce iron-containing red blood cells (RBCs).

Screening

All patients with CKD should be screened for anemia. Although the anemia may be solely related to CKD other causes should be excluded including occult GI bleeding and nutritional deficiencies such as B12 and folate. Iron status testing includes serum iron, total iron-binding capacity (TIBC), percent transferrin saturation (TSAT), serum ferritin.

Adverse Effects

Left untreated anemia can have adverse effects on cardiac function, CKD progression, and survival.[4-7] Anemia has also been shown to be an independent predictor and risk multiplier for increased mortality in CKD patients who have not progressed to ESRD. Patients diagnosed with CKD and anemia have a risk of death that is equivalent to that in patients diagnosed with both diabetes and congestive heart failure combined.[5-8] Treatment of iron deficiency anemia in CKD stages 1 through 4 may be critical to reducing associated cardiovascular morbidity and mortality since anemia-associated left ventricular hypertrophy may be irreversible if therapy is delayed until the beginning of dialysis.[9]

Treatment

The treatment of anemia of CKD includes transfusion support, erythropoietin stimulating agents (ESA) and iron therapy. Evidence suggests that aggressive treatment of iron deficiency anemia earlier in the progression of CKD can improve quality of life (QOL) as well as disease outcome and may possibly slow the progression to complete renal failure.[10-13]

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IV should be considered in anemic CKD patients who have a TSAT ≤20 percent and/or a serum ferritin concentration ≤100 ng/mL as these patients are likely to have decreased iron stores. Those with a TSAT between 20 and 30 percent and ferritin between 100 and 500 ng/may also benefit if the Hb is low enough that a higher value is desired of to try to avoid the use of ESA, Individuals with a TSAT >30 percent would not be expected to benefit. We do not routinely administer iron to patients with ferritin levels >500 ng/mL, although each patient should be individually assessed.

Results from the Dialysis Patients' Response to IV Iron with elevated ferritin (DRIVE) study suggested that iron therapy may lead to increases in hemoglobin levels and reduced ESA requirements even in patients with serum ferritin levels in excess of 500 µg/L.[14]

Dosing

There are a number of options available for treatment including oral iron which can be tried but many patients find intolerable as well as the concern for limited absorption. There are multiple intravenous iron preparations available including ferumoxytol, iron sucrose, ferric gluconate in sucrose complex, ferric carboxymaltose, and low-molecular-weight iron dextran. All of these products are equally effective in treating iron deficiency.[15]

In 2014, the Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) seemed to validate an association between high intravenous iron doses and mortality. The DOPPS results suggested that case-mix-adjusted mortality was higher when monthly doses of intravenous iron exceeded 300 mg. Hospitalization risk was also elevated. The authors called for a well-powered clinical trial to evaluate the safety of different IV iron-doing strategies in hemodialysis patients.[16]

The results of just such a trial was published in late 2018. The Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial compared 400 mg monthly of IV iron sucrose administered proactively unless the ferritin was > 700 ng/ml or the transferrin saturation was > 40% to low dose iron sucrose, 0-400 mg monthly for ferritin < 200 ng/ml or transferrin saturation less than 20%. The proactive, high dose regimen was found to be non-inferior for the primary endpoint of a composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death, assessed in a time-to first-event analysis. The high-dose regimen resulted in a reduction in the dose of erythropoiesis-stimulating agents required, no difference in infection rates, a lower rate of hospitalization for heart failure and a lower rate of transfusion.[17] The authors concluded: "Given the absence of harm that was observed with the high-dose intravenous iron regimen in our trial, the safety and efficacy of even higher doses of iron might be explored in further trials."

Intravenous iron remains a mainstay of anemia management in patients with CKD and ESRD. In earlier stage CKD, anemia can often be managed with IV iron alone. When an ESA is required to maintain an adequate hemoglobin level, a lower dose will be required when adequate, proactive IV iron is given.

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