Current and Emerging Drugs in the Treatment of Anemia in Patients with Chronic Kidney Disease

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ABSTRACT - Anemia is a common complication of chronic kidney disease (CKD), and its prevalence has shown a tendency to increase in many countries. Anemia is associated with incident heart failure and increases mortality in CKD patients, garnering public attention. Here, we reviewed recent studies about CKD with anemia, and tried to summarize the risks and causes and new progress in the treatment of renal anemia. Among the risks and causes, calcium and phosphorus metabolism disorders should be pointed out along with common causes such as iron and erythropoietin deficiencies, hypoxia, inflammation and uremic toxins, and so on. The new anti-anemia treatments mainly include hematopoietic materials supplementation, erythropoietin-stimulating agents, calcium and phosphorus regulators and hypoxia-inducible factor prolyl hydroxylase inhibitors.

INTRODUCTION

Renal anemia is a common and significant complication of chronic kidney disease (CKD), and has a high prevalence in many countries [1-4]. The 2012 KDIGO Clinical Practice guidelines suggest that anemia be defined as a hemoglobin level less than 130 g/L in males or 120 g/L in females over 15 years old [5]. Renal anemia is not independently associated with the baseline cognitive function or a decline in CKD [6], but is strongly associated with a rapid decline in the estimated glomerular filtration rate (eGFR) [7]. It is also an independent risk factor for incident heart failure [8], and of all-cause mortality in CKD patients [9]. The recommended target level of hemoglobin is 115 - 130 g/L in adult CKD patients [5]. However, treatments for anemia also carry risks.

In this review, we summarize the causes of anemia in patients with CKD (Figure 1) and recent therapeutic regimens, trying to provide useful information for nephrologists about current and emerging drugs in the treatment of renal anemia.

RISKS AND CAUSES

Hematopoietic material deficiencies

Blood loss tends to result in iron deficiency because of the edematous gastrointestinal tract and hemodialysis.

Iron deficiency is the most commonly encountered reversible cause of anemia or worsening anemia in CKD patients [10]. It is believed that transferrin saturation, serum hepcidin and plasma neutrophil gelatinase-associated lipocalin were associated with renal anemia [11, 12]. This hypothesis explains that *Helicobacter pylori* (HP) infection may influence iron stores, but no significant effect on iron deficiency anemia is observed in HD patients with or without HP infection [13].

In end-stage renal disease (ESRD) patients on maintenance dialysis, folate deficiency, which manifests as megalocytic anemia, occurs mainly because of inadequate intake, rather than dialysis-related loss or increased requirements during recombinant human erythropoietin (rhEPO) treatment. Folic acid supplementation was found to benefit hyporesponsiveness to rhEPO in elderly HD patients with folic acid deficiency anemia [14].

Calcium and phosphate abnormalities

In advanced non-dialysis-dependent CKD (NDD-CKD) patients, circulating levels of calcium and phosphorus are strongly associated with anemia [15], and not coincidentally, $25(OH)D_3$ has been reported to be correlated with ESRD [16]. Parathyroid hormone (PTH) has a direct toxic effect on EPO, and beyond that, it can cause aggravation of anemia via myelofibrosis. Brancaccio et al found that erythrocyte hematocrit levels could be increased after parathyroid resection in uremic patients [17].

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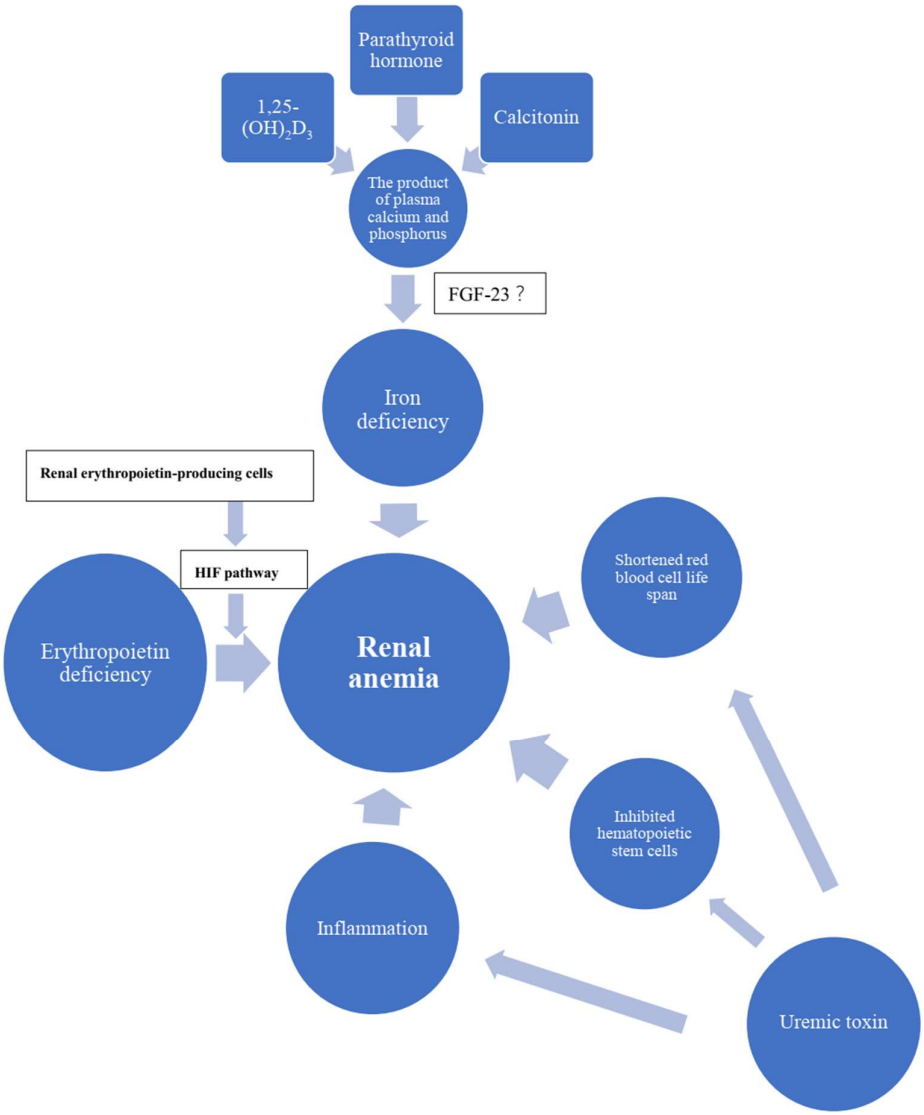

Figure 1. The potential causes of anemia in patients with chronic kidney disease

Phosphate plays a vital role in cellular energy metabolism, cell proliferation and nucleic acid synthesis. Calcium and phosphorus are absorbed in the intestinal tract and excreted by the intestine and kidney. Calcium phosphate is a component of bones, and is formed by coupling calcium and phosphorus in the body. Normally, the concentration of the product of plasma calcium and phosphorus is 35-40 mg/100 ml. When the product increases, bone formation is promoted, and calcium phosphate can even can be found in soft tissues, or specifically, in arteriosclerotic vascular diseases, when the product increases up to 70 mg/100 ml. Conversely, the absorption of bones will be accelerated, calcification will be inhibited, and finally osteochondrosis will ultimately occur when the product is reduced. The product of calcium and phosphorus can be influenced by 1,25-$(OH)_2D_3$, PTH, and calcitonin. 25-$(OH)D_3$ is activated into 1,25-$(OH)_2D_3$, and the latter can promote the absorption of calcium and phosphorus and inhibit the secretion of PTH, by 1α- hydroxylase in the kidney. PTH can stimulate the activation of 1,25-$(OH)_2D_3$, raise the calcium levels and promote phosphorus excretion, while calcitonin inhibits the activation of 1,25-$(OH)_2D_3$ and absorption of calcium and phosphorus. During ESRD, the kidney is severely damaged,

resulting in a significant reduction in the level of 1,25-$(OH)_2D_3$, unrecoverable abnormal concentrations of calcium and phosphorus and increased PTH levels, which leads to secondary hyperparathyroidism [18]. In a study among a large diverse population, higher serum phosphorus levels, which may influence hematopoiesis, should probably be blamed for anemia in early CKD or with normal kidney function [19]. Elevation of fibroblast growth factor 23 (FGF23), which is known as the major phosphate regulatory hormone, is also associated with a decline in hemoglobin over time and the development of anemia in CKD patients [20]. FGF23 levels are negatively related to hemoglobin levels during stage 3 or 4 of CKD, which may be partially mediated through the effects of aldosterone [21].

Interestingly, FGF23 seems ambiguously related to iron deficiency. In renal transplant recipients, the levels of C-terminal FGF-23 have been found to be increased in the presence of iron deficiency, and the state of iron deficiency can promote the production and cleavage of intact FGF23 into C-terminal FGF23 [22]. There is reason to believe that iron deficiency may be involved in dysregulation of the intracellular FGF23-processing mechanism, but whether iron supplementation impacts the level of FGF23 is still controversial. A prospective study observed that oral ferric citrate hydrate could decrease serum intact FGF23 and C-terminal FGF23 levels and increase intact serum PTH levels, but with phosphate and $1,25(OH)_2D$ were unchanged in HD patients [23]. Another study showed that iron supplementation failed to affect the intact and C-terminal FGF23 (i:cFGF23) ratios in CKD patients [24]. In NDD-CKD patients with normophosphatemia and ID, treatment with ferric citrate hydrate decreased PTH levels rather than serum FGF23 levels [25].

The reduction in 1,25-$(OH)_2D_3$ leads to a weakened inhibitory effect on aluminum deposition which can combine with phosphorus but at the same time, inhibit bone formation and bone mineralization, leading to aluminum-related bone disease [18]. Though there has been continuous improvement of hemodialysis systems and advances in phosphate-binding medications, aluminum toxicity, should be considered with daily supplies such as aluminum utensils for cooking in HD patients [26].

Erythropoietin deficiency

Erythropoietin deficiency is largely responsible for renal anemia. Under normal circumstances, renal erythropoietin-producing (REP) cells which act as sensors to increase EPO secretion by sensing the oxygen drop, are located in the marginal medullary area of the renal cortex. During the development of CKD, REP cells stop producing EPO, dedifferentiate and participate in renal fibrosis [27], and renal fibrosis will impact EPO production in turn.

Hypoxia inducible factor (HIF) pathway

HIFs regulate the gene expression to promote the body's adaptation to hypoxia, which is signal for angiogenesis, erythrogenesis and glycolysis [28], and specifically, the expression of the EPO gene in the kidney via the PHD2-HIF-2α pathway [29]. Under hypoxic conditions, HIF-2 regulates EPO synthesis in the kidney and liver, thus stimulating erythrogenesis [30]. Characterized as fibroblasts, pericytes and neurons, REP cells may have correlative functions. It is premised that REP cells could function as neurons, integrating the information on blood oxygen concentration and local oxygen consumption from sensing tissue pO_2, and thereby regulate EPO secretion [27]. Additionally, HIFs activate a set of genes involved in ferric absorption and transport, increasing the intestinal iron uptake, promoting iron transport to tissues, and downregulating hepcidin [31].

Inflammation

Anemia and inflammation are common in peritoneal dialysis (PD) patients, and anemia is suggested to correlate with inflammation in PD patients [32]. However, another study showed no association between blood cell life span and inflammatory biomarkers, such as interleukins-6,18,and 10 and high-sensitivity C-reactive protein [33].

Uremic toxins

Red blood cell life span is positively correlated with levels of uric acid and blood urea nitrogen [33] and CKD progression [34]. In CKD stage 3/4 or HD patients, uremic toxins increase erythrophagocytosis by increasing eryptosis and promoting a proinflammatory monocyte phenotype [35]. In addition, the numbers of CD55- and CD59-deficient red blood cells are significantly higher in CKD patients than in controls [36], though the red blood cells are usually positive in paroxysmal nocturnal hemoglobinuria. As a natural inhibitor of pluripotent hematopoietic stem cell proliferation, N-acetyl-seryl-aspartyl-lysyl-proline accumulates due to CKD, which ultimately leads to anemia [37]. Controversially, uremic toxin concentrations, such as indole 3-acetic acid, paracresyl sulfate and indoxyl sulfate, are

detected, showing no association with anemia parameters in HD patients [38].

Other causes and risks

In addition to the abovementioned factors, an unavoidable cause of anemia is chronic blood loss, including hemorrhaging trends and blood residue in dialyzers during hemodialysis. A cohort study identified a number of independent risk factors for anemia, such as CKD stage, body mass index, smoking, leukocyte count, serum albumin, phosphorus concentration, calcium, and iron markers [39]. In addition, albuminuria is observed as one of the significant risk factors for eGFR [9], which is inextricably linked with renal anemia. In NDD-CKD patients, blood manganese levels are positively associated with Hb levels as well [40]. Serum adiponectin, an adipokine secreted by adipocytes, is considered to be associated with anemia development in CKD. A higher serum adiponectin level is reported to be independently associated with a low hemoglobin level [41].

TREATMENT

While transfusion is not favorable, treatment with antianemia medications, although well accepted, nevertheless comes with risk in HD patients with anemia [42]. It is important to maintain stable antianemic drug concentrations for erythron response in dialysis patients and monitor the fluctuations in concentration, as the high variability of anti-anemic drugs will lead to a less successful erythron response [43]. Recent anti-anemia therapies are summarized as follows.

Hematopoietic material supplementation therapy

Oral iron supplementation via ferrous citrate iron is well-tolerated and efficient in IDA and CKD patients, regardless of NDD-CKD or hemodialysis-dependent CKD (HDD-CKD) [25, 44]. However, the optimal administration route and frequency of drug application are still being determined. It was reported that only 21.6% of anemic patients achieved an increase in Hb of at least 1 g/dL via oral iron administration [45], while intravenous iron therapy may be an alternative for nonresponders using oral iron therapy [46]. Kalra et al hold the opinion that intravenous iron therapy is well tolerated and more efficacious than oral iron to increase Hb levels [47]. It is believed that intravenous iron therapy is not only effective and tolerated, but also helpful for lowering erythropoietin-stimulating agents (ESA) doses [48]. Ishida et al considered that intravenous iron can be administered for bacterial infection in HDD-CKD patients, although this treatment is deprecated by anemia guidelines for CKD [49]. In contrast, others think that risks of serious adverse events, including infectious diseases and cardiovascular events, are relatively increased in NDD-CKD patients on intravenous iron therapy [50]. The liver iron concentration was reported to be elevated during standard intravenous iron supplementation in HDD-CKD patients [51]. Concerning the issue of frequency of ESA application, intermittent intravenous iron administration is more highly recommended than continuous administration for stable antianemia efficacy in patients on maintenance hemodialysis [52]. Hepcidin is the key regulator of iron homeostasis. Hepcidin-25 was considered a significant predictor of erythrocytopoiesis response after intravenous iron therapy in CKD patients [53], while an RCT showed that neither the baseline level nor the change in hepcidin was able to predict response to iron therapy in NDD-CKD patients [54].

Folic acid and vitamin B12 deficiencies are important causes of anemia; however, supplementation with vitamins seems unessential for improving anemia but is associated with delaying the progression of CKD and reducing cardiovascular risks in CKD patients [14, 55, 56].

Calcium and phosphorus metabolism regulation

Cinacalcet, a drug used in the treatment of hyperparathroidism secondary to CKD, suggests an additional benefit in the management of anemia in HDD-CKD patients [57] via PTH pathways [58]. Iron-based phosphate binders, represented by sucroferric oxyhydroxide and ferric citrate, are gradually emerging. In HDD-CKD patients who were receiving antihyperphosphatemic drugs with poor dephosphorizing effects, the administration of sucroferric oxyhydroxide had lower serum phosphorus and FGF-23 levels and a higher hemoglobin concentration compared to those without sucroferric oxyhydroxide treatment [59]. There were 441 patients on dialysis who were randomly assigned to two groups, with one group treated with ferric citrate and the other treated with sevelamer, calcium acetate or both. Over 52 weeks, no significant difference was seen in the mean serum phosphorus level, but increased mean hemoglobin levels and red blood cell mean cell volume were statistically significant in the ferric citrate group. Then, the ferric

citrate group was sequentially rerandomized into two groups, a ferric citrate group and a placebo group. After 1 month of treatment, the ferric citrate group presented a lower mean serum phosphorus level than the placebo group. A conclusion was drawn that ferric citrate could decrease serum phosphorus as well as improve anemia [60]. In NDD-CKD patients, ferric citrate is also effective in reducing FGF23 and improving renal anemia [61]. Currently, sucroferric oxyhydroxide and ferric citrate have been approved for marketing in the United States.

Erythropoietin stimulating agents (ESAs)

ESAs may have renoprotective effects and slow the progression of CKD [62]. Long-acting ESAs tend to be more effective and stable than short-acting ESAs in treating anemia [63], and a fixed dose of long-acting ESAs at a higher frequency can improve appetite, reduce inflammation and correct anemia in patients on hemodialysis [64]. For predialysis patients with CKD, long-acting ESAs may be more useful, because of the lower frequency of hospital visits [65]. Darbepoetin, a newer ESA with a longer half-life than rhEPO, split into "mini-doses", or fixed small doses, and used at a frequency of twice-monthly or once a month is effective in CKD patients [66, 67]. Individualized dosing of ESAs through a computer-designed dosing system, can facilitate improvement in Hb levels, decrease Hb variability and reduce the dose of ESAs required to achieve target [68]. Subcutaneous epoetin is associated with a lower dose of ESAs and lower risks of death and hospitalization than intravenous administration in HD patients [69].

The Hb level usually fluctuates widely in ESA-treated HDD-CKD patients, which fortunately, has been reported to have no significant impact on mortality and hospitalization rates [70]. ESAs have similar anemic control in patients either with or without transplantation owing to chronic ESA rejection, though those with transplantation were supposed to have a more severe anemic state because of immunosuppression [71]. In a randomized, placebo-controlled trial with a 2-year follow-up, the renal function of patients with moderate CKD or with previous kidney transplantation was observed to be stable in the absence of low-dose ESAs, and early low-dose ESA therapy showed no significant effect on the amelioration of proteinuria [72]. Nakhoul et al reviewed the complicated and conflicting evidence on the treatment of renal anemia and held that ESAs should be individually prescribed according to the severity of anemia or stages of CKD to reduce the risk of cardiovascular events [73]. The initiation of ESA therapy is suggested when Hb levels decrease to 10 - 11 g/dL in nondialysis CKD patients [74, 75].

The 2012 KDIGO clinical guidelines practice claims that the recommended target level of hemoglobin is 115 - 130 g/L in adult CKD patients. Higher Hb levels have been found to be associated with higher mortality in CKD patients, and higher ESA doses are accompanied by a 1.2-1.5-fold increased risk of mortality [76]. A prospective cohort study showed that ESA hyporesponsiveness is associated with an increased risk of all-cause mortality in patients treated with HD [77]. ESA hyporesponsiveness may be related to the interaction between ESAs and statins [78], ACE gene polymorphism [79] and inhibition of erythropoietin receptor expression [80], which accounts for increasing doses of ESAs, and finally sets up a vicious circle of worsening responsiveness. Higher ESA doses resulted in higher mortality. Thus, the safety of high doses of ESAs has been questioned. An estimated EPO dose of 66.5 IU/kg/wk was suggested for each 1 g/dL Hb level below the target, and the feasible maintenance dose was 8000 IU/wk among HD patients [81]. Adequate dosages of iron preparations and ESA were suggested to be helpful in preventing cardio- and cerebrovascular events [82], and lower than normal doses (150 - 300IU) were more appropriate when Hb levels were greater than 11 g/dl [83]. A study found that iron supplementation maintaining serum ferritin levels between 500 and 1200 ng/ml might help improve erythropoietin reactivity [84]. The standard dose remains inconclusive. V-J combinations of T-cell receptors have been reported to be helpful in predicting EPO responses in ESRD patients [85]. Erythropoietin-resistant anemia is associated with cardiovascular events in ESRD patients. As shown in a longitudinal study, inflammatory state, low serum iron reserve, continuous usage of ARBs and poor nutritional status are related risks in epoetin α resistance in HD patients [86]. Higher doses of rhEPO are required in ESRD patients with increased serum IL-17 and IFN-γ levels [87]. C-reactive protein is a determining factor of ESA resistance in HD patients [88]. The platelet/lymphocyte ratio can be used as a predictive value in HD patients with erythropoietin resistance [89].

Hypoxia inducible factor prolyl hydroxylase inhibitor (HIF-PHI)

HIF-PHIs are an emerging drug class in the treatment of anemia with CKD. As a HIF stabilizer, HIF-PHIs simulate the hypoxic state of the body, increase endogenous EPO levels and coordinate iron utilization [90]. Vadadustat, roxadustat and daprodustat are representatives HIF-PHIs, and they have entered into clinical trials. All of them seem effective and safe, and have potential in the treatment of anemia with CKD in both NDD-CKD and HDD-CKD patients [91-99]. However, in our previous meta-analysis, HIF-PHIs were only effective in NDD-CKD patients [100]. Because of their connection with TGF-β and VEGF, the issue of whether HIF-PHIs cause renal fibrosis remains unknown. HIF-PHIs are a topic of considerable interest in the treatment of renal anemia, but their safety and tolerability should be assessed cautiously [101, 102].

Other treatments

L-carnitine may help increase hemoglobin and reduce erythropoietin usage by its antioxidant and anti-inflammatory effects [103]. Endoscopy is recommended for the early identification of gastrointestinal lesions, particularly adenomatous polyps and colorectal cancer, which may have an effect on anemia in CKD patients [104]. Excluding the disadvantage of albumin removal, a more permeable dialysis membrane is suggested for its potential impact on ESA resistance in HD patients [105]. Renal outcomes were independent of the patient/registered nurse ratio [106].

CONCLUSION

In conclusion, anemia is a common, mortality-related and increasing complication of CKD. CKD stage, body mass index, smoking, leukocyte count, serum albumin, phosphorus concentration, calcium, and low 25-$(OH)D_3$ and 1,25-$(OH)_2D_3$ levels are thought to be independent risk factors of renal anemia. Hematopoietic material deficiency, calcium and phosphorus metabolism disorder, EPO deficiency, hypoxia, inflammation and uremic toxins may be involved in the mechanism or progression of anemia in CKD. Correction of anemia conditions can lower mortality and hospital admission rates. Antianemia drugs mainly include hematopoietic material supplementation, ESAs, calcium and phosphorus regulators, and HIF-PHIs. However, much remains unknown and controversial. The treatment of renal anemia still has a long way to go.

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