Cardiorenal Anemia Syndrome in Chronic Kidney Disease

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Anemia is a frequently encountered problem of chronic kidney disease (CKD) and deteriorates as renal function declines. Anemia increases the risk of death in CKD patients with diabetes and hypertension, which are the 2 leading causes of CKD. Recent studies suggest that correction of anemia improves patient quality of life and may delay the progression to end-stage renal disease. Anemia is often only treated in the late stages of CKD or after the initiation of renal replacement therapy. Thus, anemia of CKD is often unnoticed and lacks appropriate treatment. To practically manage high-risk patients with CKD and its associated cardiovascular diseases, it is mandatory to diagnose and appropriately treat anemia of CKD earlier. The optimal level of hemoglobin for greatest clinical benefit is unclear, but at present, it is recommended to remain ≥ 11 g/dL. This paper provides recommendations for the diagnosis and management of anemia associated with CKD based on international practice guidelines. [*J Chin Med Assoc* 2007;70(10):424–429]

Key Words: anemia, cardiovascular disease, chronic kidney disease, erythropoiesis-stimulating agent

Introduction

Anemia is frequently encountered in patients with chronic kidney disease (CKD), and initiates early in the course of the disease and worsens as renal function declines.[1] Renal anemia associated with declining kidney function is mainly due to inadequate renal production of erythropoietin in response to low hemoglobin levels regardless of the etiology. While anemia in CKD is largely related to decreased production of erythropoietin by the diseased kidneys, it may also arise from chronic blood loss, or inhibition of erythropoiesis caused by inflammation, nutritional deficiencies, secondary hyperparathyroidism, or accumulation of inhibitory uremic toxins.[2] The high prevalence of anemia in CKD patients not yet on dialysis, even in the early stages, has just recently gained attention. Published data indicated that approximately 50% of patients with CKD stage 3 or 4 are anemic (defined by hemoglobin ≤ 12 g/dL), and the prevalence of anemia increases to 75% in patients reaching CKD stage 5.[3] Although a substantial number of patients with only mild kidney dysfunction are anemic, very few patients are treated with erythropoiesis-stimulating agents (ESA).[4]

Anemia in CKD when left untreated can negatively affect cardiac, cognitive and immune functions, quality of life, renal disease progression, and survival.[5,6] Moreover, it significantly adds to disease burden by triggering or aggravating the existing comorbidities. Cumulative evidence suggests that timely treatment of anemia in CKD can improve quality of life as well as disease outcome, and possibly slow down the progression of renal failure.[7,8] Since cardiovascular outcomes are poor in CKD patients, the relationship between anemia correction in CKD and cardiovascular disease (CVD) is an area of active research. Nevertheless, diagnosis and treatment of anemia in the CKD population is surprisingly low.[9] An important part of the care of CKD patients is the recognition and prompt management of cardiovascular comorbidity in order to slow the progression of renal failure and vigorously affect disease outcome. This report focuses on anemia of CKD as a common but modifiable risk factor and its role in CVD, and offers an overview of anemia treatment with

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practical guidelines for the management of anemia in CKD patients for primary care physicians.

Anemia and CVD in CKD

Cardiovascular complications remain the leading cause of death in CKD patients, and CKD is an independent risk factor for CVD. About 40% of all people with moderate to severe CKD have congestive heart failure (CHF), and this increases to 60% by the time patients reach ESRD.[10] Anemia has been associated with the development of new-onset CHF, and increases the risk of hospitalization for myocardial infarction and CHF, and progression to dialysis.[11] When anemia is factored into the equation of renal and cardiac insufficiency, it becomes a significant risk multiplier for adverse disease outcomes.[12] The cardiorenal anemia syndrome describes the relationship between CKD, CHF, and anemia. The syndrome is a circular pattern of CKD causing anemia and CHF, with CHF leading to anemia and CKD: each condition causes or worsens the other.[13,14] Anemia is an independent risk factor for adverse cardiovascular outcomes, and anemia and CKD have a synergistic effect, increasing the risk of CVD and all-cause mortality.[15] Indeed, anemia has been referred to as the fifth major cardiovascular risk factor along with diabetes, hypertension, hypercholesterolemia and smoking.[10]

Even in the absence of heart disease, anemia can lead to abnormalities in cardiac structure and function. Peripheral ischemia in the anemic state leads to vasodilatation and reduced blood pressure. Thereafter, activation of the renin–angiotensin–aldosterone system reduces renal blood flow and glomerular filtration rate, and increases sodium and water absorption. Extracellular volume expansion from excess water retention subsequently results in hemodilution and further decrease in hemoglobin. Plasma volume overload permits additional stress on the heart and causes ventricular dilatation. In the long run, sustained increased cardiac workload contributes to left ventricular hypertrophy and myocardial cell death.[13,16] Anemia can also lead to cardiac cell death via reduced oxygen supply and increased oxidative stress.[13]

Management of Anemia of CKD

The international practice guidelines for the management of anemia of CKD clearly outline steps that can be taken to determine when and how to test for anemia, when to initiate anemia therapy, appropriate target hemoglobin levels and iron indices, and how often to assess therapeutic efficacy.[6,17]

Anemia tests should be performed in all CKD patients, regardless of stage or cause. The diagnosis of anemia should be made and further evaluation undertaken at the hemoglobin values of < 12.0 g/dL in adult females and < 13.5 g/dL in adult males. The guidelines recommend that the anemia workup include the following tests: complete blood count, absolute reticulocyte count, serum ferritin, and serum transferrin saturation (TSAT). Serum iron and TSAT reflect the amount of iron that is immediately available for erythropoiesis, and serum ferritin is a reflection of total body iron stores. TSAT < 20% and serum ferritin < 100 ng/mL are indicative of absolute iron deficiency, wherein there are insufficient stores of iron to support accelerated ESA-driven erythropoiesis. Although most patients will receive ESA in response to low hemoglobin levels, monitoring of iron status is necessary. In addition, it is important that other possible causes of anemia, such as subclinical inflammation or infections, malnutrition, chronic blood loss, secondary hyperparathyroidism and aluminum intoxication, are excluded prior to starting ESA therapy.[17,18]

The term ESA applies to all agents that augment erythropoiesis through direct or indirect action on the erythropoietin receptor (Table 1). Currently available ESAs include epoetin alfa, epoetin beta, and darbepoetin alfa. Darbepoetin alfa contains 8 additional sialic

Table 1. Structural and pharmacokinetic characteristics of erythropoiesis-stimulating agents (ESAs)

ESA	Structural characteristics	N-linked carbohydrates	Half-life (hr)*	
			Intravenous route	Subcutaneous route
Epoetin α	Identical to human (165 aa, 34 kD)	3	6.8 ± 0.6	19.4 ± 2.5
Epoetin β	Identical to human (165 aa, 34 kD)	3	8.8 ± 0.5	24.2 ± 2.6
Darbepoetin α	5 different aa from epoetin α and β	5	25.3 ± 2.2	48.8 ± 5.2
CERA	PEGylated epoetin β	3	134 ± 19	139 ± 20

**Data are presented as mean ± standard error of the mean. aa = amino acids; CERA = continuous erythropoiesis receptor activator; PEGylated epoetin β = epoetin β coupled to polyethylene glycol (PEG), being developed to overcome the shortcomings of currently approved ESAs.*

acid residues compared to epoetin alfa. Darbepoetin alfa has a lower binding affinity for the EPO receptor than does epoetin alfa, but the additional sialic acids confer a 3-fold longer serum half-life that is associated with greater biological activity.[19] Two additional ESAs are currently in phase 3 clinical trials for the treatment of anemia associated with non-dialysis CKD, ESRD on dialysis, and cancer: CERA (continuous erythropoietin receptor activator) and Hematide™. These agents differ from epoetin alfa and beta, and darbepoetin alfa in their amino acid sequence, plasma half-life, and EPO receptor binding affinity.[20,21]

Once anemia is established, ESA therapy should be initiated and supplemented with iron therapy where appropriate. K/DOQI guidelines suggest a lower hemoglobin limit of 11 g/dL in men and women with CKD. In conjunction with ESA, iron therapy should be administered to generally maintain serum ferritin > 100 ng/mL and TSAT > 20% in CKD patients not on dialysis. In patients who are receiving ESA, therapeutically, hemoglobin should be monitored at least monthly. Iron status testing should be performed every month during the initiation of ESA therapy and every 3 months once ESA therapy is stabilized.[17] Subcutaneous (SC) injection is the preferred route of administration of ESA for CKD patients not yet on dialysis. The bioavailability of SC epoetin is only about 20%, but it is absorbed more slowly than intravenous epoetin and maintains a steady, albeit lower, serum level for a longer time. Target hemoglobin levels can be maintained with a less frequent dosing schedule with SC epoetin.[22] When administering SC epoetin to adults, the K/DOQI guidelines recommend epoetin dosing twice or thrice a week to achieve a rate of increase in hemoglobin of approximately 1–2 g/dL/month to reach the target within a 2–4 month period. Epoetin dose should be reduced, but not necessarily stopped, when hemoglobin approaches 12 g/dL or increases at a rate ≥ 1 g/dL in a 2-week period. Dose titrations should be determined by hemoglobin level, the target level, the rate of increase in hemoglobin, and the clinical situation.[5,6,17] The recommended starting dose for epoetin alfa is 50–100 U/kg thrice a week; however, recent reports have shown that hemoglobin can be increased and adequately maintained by dosing weekly or even every 2–4 weeks.[6,17,23] Darbepoetin alfa is the only long-acting ESA currently available in Taiwan, and its half-life is approximately 3 times longer than that of epoetin alfa. The recommended starting dose of darbepoetin alfa is 0.45 μg/kg once weekly to obtain adequate hemoglobin levels, but some patients may be able to reach target hemoglobin level with 1 dose every 2 weeks, and the maintenance doses are often lower.

Provision of sufficient available iron is a prerequisite to ensure the optimal response to ESAs. To begin ESA therapy, TSAT and ferritin levels must be at least 20% and 100 ng/mL, respectively.[6,17,18] The most convenient way to receive iron therapy is orally for adult CKD patients, and the recommended daily dose is at least 200 mg elemental iron. Absorption of oral iron is poor, however, and may require multiple smaller doses scheduled around mealtimes for optimal absorption, and many patients experience unwanted side effects such as nausea and vomiting. Intravenous iron may be appropriate for some CKD patients. Although inconvenient, intravenous iron is thought to improve the responsiveness to ESAs and may reduce the requirements of ESA dose to achieve and maintain adequate hemoglobin levels in CKD patients.[5,6,17] Iron overload is rare, but routine administration of iron when serum ferritin is > 500 ng/mL is not recommended.[17] Iron can accumulate in organs such as the heart and liver, but there is inconsistent evidence as to its significance and pathology.[24] Functional iron deficiency may be present when serum ferritin is > 500 ng/mL (reflecting adequate iron stores) and TSAT is < 20% (reflecting an inappropriate amount of iron available for erythropoiesis), however, these patients may benefit from a course of iron therapy.

Preserve Cardiovascular Function by Establishing Optimal Goals for Anemia

Data suggest that the normalization of hemoglobin has no clear effect on the development or progression of left ventricular hypertrophy, and in some cases, increases the risk of cardiovascular events or death.[25–27] Recently, 3 large randomized trials designed to examine the effect of hemoglobin normalization in CKD patients not on dialysis have reported no benefit, or increased risk for cardiovascular outcomes associated with higher hemoglobin targets (Table 2). In the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE) trial, there were no significant differences between a high hemoglobin target (13–15 g/dL) and a low hemoglobin target (10.5–11.5 g/dL) in overall mortality, and left ventricular mass index. Interestingly, a slightly but significantly larger number of patients with high hemoglobin targets progressed to dialysis by the end of the study than did those with low hemoglobin targets, suggesting that a higher hemoglobin level does not slow the progression of renal disease.[28] In the European trial ACORD (Anemia Correction in Diabetes), patients assigned to a higher hemoglobin target (13–15 g/dL)

Table 2. Summarized results of clinical trials of high compared with low hemoglobin (Hb) or hematocrit (Hct) values in patients with chronic kidney disease

Trial	ESA	Target Hb/Hct values	End points				
			Mortality	CV events	Quality of life	ΔLVMI	GFR decline rate
Normal hematocrit study	Epoetin α	Normal Hct 42% *vs.* low Hct 30%	RR for normal *vs.* low Hct: 1.3 (95% CI, 0.9–1.9)		Improvement		
CREATE	Epoetin β	Normal Hb 13–15 g/dL *vs.* low Hb 10.5–11.5 g/dL		HR for normal *vs.* low Hb: 0.78 (95% CI, 0.53–1.14; $p = 0.20$)	No improvement	No difference	No difference
CHOIR	Epoetin α	High Hb 13.5 g/dL *vs.* low Hb 11.3 g/dL		HR for high *vs.* low Hb: 1.34 (95% CI, 1.03–1.74; $p = 0.03$)	Improvement, but similar in 2 groups		HR for high *vs.* low Hb: 1.19 (95% CI, 0.94–1.49; $p = 0.15$)
ACORD	Epoetin β	Normal Hb 13–15 g/dL *vs.* low Hb 10.5–11.5 g/dL			Improvement	Decline, but no difference between 2 groups	No difference

ESA = erythropoiesis-stimulating agent; CV = cardiovascular; ΔLVMI = change in left ventricular mass index; GFR = glomerular filtration rate; RR = relative risk; CI = confidence interval; HR = hazard ratio.

experienced a significant increase in quality of life compared to patients assigned to receive epoetin beta only when hemoglobin fell below 10.5 g/dL; however, there was no difference between the 2 groups in the change in left ventricular mass index (the primary end point) after 15 months.[29] The CHOIR (Correction of Hemoglobin and Outcomes in Renal Disease) trial was prematurely terminated because of the increased risk of cardiac events associated with normalization of hemoglobin. In this trial, targeting a higher hemoglobin level (13.5 g/dL) was associated with increased risk of death, myocardial infarction, and hospitalization for heart failure and stroke compared to partial anemia correction (target hemoglobin 11.3 g/dL).[30] Recently, a meta-analysis of 9 clinical trials further demonstrated an increased risk for all-cause mortality in the high hemoglobin target groups compared to the low hemoglobin groups.[31]

Treatment of anemia in CKD patients can result in a significant increase in several measures of health-related quality of life, including cognitive function.[32] Despite conflicting results on the appropriate level of anemia correction for an optimal reduction in cardiac end points, it is clear that anemia confers a significant risk of cardiovascular morbidity and mortality in patients with CKD, suggesting that there is much to learn regarding the use of ESA in CKD patients. While recent data suggest that more conservative hemoglobin targets (11–12 g/dL) may carry less risk than full correction of anemia (hemoglobin targeted to ≥ 13 g/dL), future clinical trials will be needed to more thoroughly examine the use of ESA in these patients, including when to initiate therapy, the proper ESA dose, and, most importantly, the optimal hemoglobin target.

Larger trials and additional long-term data on the effects of ESA on comorbid risk reduction and the preservation of renal function in CKD patients not on dialysis are needed. The TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) study is designed to determine the impact of anemia therapy with darbepoetin alfa on mortality and non-fatal cardiac events and renal disease progression in CKD patients with type 2 diabetes. Patients will be randomized to 2 study arms: patients in the treatment arm will receive darbepoetin alfa to a target hemoglobin of 13 g/dL, and patients in the control arm will receive placebo when hemoglobin is ≥ 9 g/dL, or darbepoetin alfa when hemoglobin falls below 9 mg/dL until hemoglobin reaches ≥ 9 g/dL again. The primary end point is a composite of the time to all-cause mortality and cardiovascular events. The secondary end points will assess the effect of anemia correction on renal disease and quality of life, and include the time to ESRD and

changes in the rate of decline of estimated glomerular filtration rate.[33]

The level of anemia correction and its impact in CKD patients is an issue that is being actively debated and will be clarified further by the results of the TREAT trial. What will be of particular interest are the renal and cardiovascular effects of maintaining what is considered a relatively low hemoglobin level (between 9 and 10 g/dL), in contrast to previous studies that targeted higher hemoglobin levels (> 13 g/dL). The results of this trial may provide insight into the optimal range of hemoglobin in CKD patients not yet receiving dialysis that will preserve cardiovascular structure and function and delay renal disease progression.

Anemia starts early in the course of CKD and gets worse as kidney function declines. Anemia of CKD is a risk multiplier for CVD, and cardiovascular complications are the most important cause of death in CKD patients. Since anemia is easily diagnosed and typically amenable to treatment, an assessment should be performed early in all CKD patients so that plans for anemia management can be initiated based on the established international guidelines. Evidence suggests that ESA therapy can reduce the morbidity and mortality associated with CKD, slow the progression of renal failure, and improve patient quality of life. The international practice guidelines recommend that target hemoglobin should be ≥ 11 g/dL in CKD patients,[6,17] but there is insufficient evidence to suggest routinely maintaining hemoglobin levels at ≥ 13 g/dL in ESA-treated patients.[17] Furthermore, hemoglobin > 12 g/dL is not recommended in patients with CVD according to the *European Best Practice Guidelines*.[6] Future studies will determine the optimal hemoglobin level for outcome improvement in these individuals.

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