44 Management of Anemia in Chronic Kidney Disease

Abstract: Anemia is a frequent complication of chronic kidney disease (CKD). Anemia of CKD develops early and worsens with progressive renal insufficiency. Anemia is under recognized and undertreated. Of considerable importance, anemia is a risk factor for cardiovascular disease. The recognition of anemia in CKD patients begins with an estimation of glomerular filtration rate (GFR) <60 ml /min/1.73 m^2. The anemia is diagnosed when the hemoglobin is $\leq$ 12gm /dl in male and post menopausal women or $\leq$ 11gm/dl in premenopausal women. The causes of anemia are multifactorial, but iron deficiency and erythropoietin deficiency are the two major causes of anemia. Currently epoetin alfa and darbepoetin alfa are the two erythropoiesis stimulating agents approved for use. Adequate iron stores defined as transferrin saturation >20% and ferritin 100 microgram are also needed for appropriate increase in hemoglobin.

Key words: Erythropoiesis Stimulating Agent (ESA), Glomerular Filtration Rate (GFR). National Kidney Foundation's Kidney Disease Quality Initiative (NKF-K/DOQI).

INTRODUCTION

Anemia is a common major manifestation of chronic kidney disease (CKD).[1] The prevalence and severity of anemia worsen steadily as CKD advances. More than 80% of patients have anemia when the glomerular filtration rate (GFR) falls significantly.[2]

The incidence and prevalence of the disease have doubled in the past decade most likely because improved treatments for hypertension, diabetes mellitus and coronary artery disease have improved longivity in affected patients and their likelihood of developing CKD.[3]

Anemia associated with CKD is under recognized and under treated. This is of concern, since almost three fourths of the patients presenting for dialysis have a hemoglobin level lower than 11 gm/dl. This may be the result of not only the poor recognition of anemia but also poor recognition of CKD itself.[4]

As renal function starts to decline, so does hematocrit; the decrease in hematocrit is more gradual in the early stages and faster in the later stages of kidney disease.[5]

The National Kidney Foundation (NKF) defines CKD as glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 (body surface area) for three months or more.[6] This GFR rate corresponds with a serum creatinine concentration higher than 1.5 mg/dl in male and higher than 1.3 mg/dl in women.[6] CKD can also be defined by the presence of urinary albumin in an excretion rate higher than 300 mg/24 hours or in a ratio of more than 200 mg of albumin to 1 gm of creatinine.[6]

There is a dilemma in diagnosing anemia in CKD using the hemoglobin level, due to lack of single accepted level of hemoglobin that defines anemia. In the United States, NKF's kidney disease outcomes quality initiative (NKF- K/DOQI) recommends anaemia workup when the hemoglobin is <12gm/dl in adult men and post menopausal women or less than 11gm /dl in prepubertal children and premenopausal women. The European best practice guidelines identify anemia when the hemoglobin level drops below 13.5 gm/dl in women. The World Health Organization (WHO) defines anaemia as haemoglobin level below 13 gm/dl in male older than 15 years, below 12 gm/dl in women older than 15 years, and below 11gm/dl in pregnant women. No differentiation is made for elderly or menopausal status. WHO has pointed out that hemoglobin levels vary not only with age and sex, but also with altitude, smoking, and perhaps

genetic factors. WHO also advices considering that high altitude and smoking can raise hemoglobin. For example, hemoglobin of 12.5 g/dl in women who smoke and live in mountains could easily mask anemia.[7]

CAUSES OF ANEMIA IN CKD

When a patient develops CKD, anemia develops as a result of any one or the combinations of multiple factors, like decreased erythropoietin (EPO) production, bone marrow suppression by uremia, shortened red blood cell life span, blood loss, deficiency of vitamin B_{12} and/or folate, iron deficiency, inflammation, infection, osteitis fibrosa cystica secondary to hyperparathyroidism in CKD and aluminium toxicity.

The evidence suggests that as renal function is lost in CKD, the kidney produces less erythropoietin, which is essential to stimulate the bone marrow to produce RBCs. Additionally, uremia is associated with shorter life span of RBCs from 4 months to 30 to 40 days. Presence of uremia toxins such as polyamines also leads to suppression of RBC production. Further, secondary hyperparathyroidism may develop and fibrosis of bone marrow can ensue. In addition, more than a third of the people with CKD become iron deficient; in some, the iron deficiency results from a decline in platelet function resulting in loss of blood from gastrointestinal tract. In CKD, increased inflammatory cytokines, common in chronic diseases, can also block iron release from reticuloendothelial system, causing a "functional" iron deficiency.

While several factors contribute to anemia associated with CKD, most important factors responsible for anemia are deficiency of erythropoietin production and iron deficiency.[8]

CONSEQUENCES OF CKD RELATED ANEMIA

The clinical consequences of anemia have been studied more in CKD than in any other disease state. The condition affects almost every organ system. In addition to contributing to the development of left ventricular hypertrophy (LVH), anemia impairs cognitive function, decreases exercise capacity, deteriorates quality of life, and may weaken immune response.

In patients with end stage renal disease (ESRD), severe anemia is associated with increase in hospitalization, health care costs, and mortality.

Cardiovascular disease (CVD) is the cause of death in nearly half of the dialysis patients. Many of the risk factors for CVD are also risk factors for CKD, including hypertension, diabetes, and male gender. Complications of CKD create additional cardiovascular risk factors, such as volume overload, anemia, increased oxidant stress, hypoalbuminemia, hypokalemia, hyperkalemia, and metabolic acidosis.

LVH is a common finding in patients with CKD, resulting from alteration in left ventricular wall stress caused, at least in part, by hypertension and anemia. It has been shown to progress with degree of CKD. LVH is a significant risk factor for cardiovascular events independent of blood pressure in hypertensive men, and for cardiac and all cause mortality in patients who require dialysis or kidney transplantation.[9-11]

DIABETES, CKD AND ANEMIA

Anemia is unrecognized and largely untreated in patients of diabetes. Anemia is associated with increased risk of diabetic complications. A number of mechanisms such as predominant damage to EPO producing specific cells and vascular architecture of tubulointerstitial cells, autonomic neuropathy, urinary EPO loss, celiac disease (Type 1 diabetes), drug therapy (ACE inhibitors, thiazolidinediones) are the possible factors to cause anemia in CKD in diabetes. Thickening and reduplication of tubular and epithelial basement membrane of EPO producing cells even in absence of microalbuminuria and in normoalbuminic patients is largely the result of increased vulnerability of renal microcirculation in diabetes, due to hyperglycemia, increased capillary

pressure and proteinuria. The damage results in peritubular fibrosis which affects the secretory mechanism of EPO producing peritubular cells. But in early stage of the disease, it is the sensing mechanism of peritubular cells that is affected rather than the secretory mechanism. Autonomic neuropathy may be responsible for this early loss of sensing mechanism of the peritubular cells.

Another important observation is, anemia in diabetes can lead to false low HbA1c leading to under treatment of diabetes which in turn contributes to progression of diabetic complications.[12-14]

EVALUATION OF ANEMIA IN CKD

According to the NKF–K/DOQI guidelines when stage 3 CKD is identified (GFR $\leq$ 60 ml/min/1.73 m^2), it is immediately necessary to assess the hemoglobin level (since it is accepted that hemoglobin has already been checked earlier). The hemoglobin value is generally preferred and accepted to assess anemia rather than hematocrit as it is a measured value. Hematocrit may be altered by shift of plasma water. If the hemoglobin is above the defined value cut off for anaemia, the clinician only need to monitor the patient until the hemoglobin level falls below the recommended value. If the hemoglobin level is <12gm/dl in a man or postmenopausal women or 11gm/dl in a premenopausal women, the NKF – K /DOQI recommends workup for anemia for the possible etiology.[15]

A. Evaluation of iron (Fe) status
    a. *Serum ferritin*: When the ferritin level is less than 100 microgram/lit, Fe deficiency is diagnosed in stage 5 CKD and considered in stage 3 and stage 4 CKD. As the serum ferritin is an acute phase reactant and frequently raised in CKD, the diagnostic cut off value is raised.
    b. *Hypochromic red cells*: Percentage of hypochromic red cells has to be more than 6% to consider Fe deficiency anemia
    c. *Transferrin saturation*: Iron deficiency is considered when the transferrin saturation is $\leq$ 20%.
    d. *Serum and total iron binding capacity*: Iron deficient state is said when serum Fe is $\leq$ 65 mg/dl in male and $\leq$ 50 mg/dl in female and TIBC is $\geq$ 425 mg/dl.[16, 17]
B. *Measurement of EPO*: EPO measurement is not routinely considered in anemia in CKD.
C. Vitamin B_{12} and Folic acid is measured when the RBC indices also show macrocyte in peripheral blood.
D. *Bone marrow aspiration*: To determine marrow fibrosis in osteitis fibrosa cystica, features of megaloblastic anemia and serum Fe in iron deficiency anemia.

TREATMENT OF ANEMIA IN CKD

Iron Supplementation

The preferred route is oral. The anemic patients are usually given at least 200 mg of elemental iron per day in three divided doses. Higher dose may be required, as the absorption of iron in CKD patients is around 10%. If oral route is not possible due to inadequate absorption or gastro-intestinal side effects, intravenous iron is given.[15,17]

Recombinant Human Erythropoietin (EPOETIN)

In 1990, Epoetin- alfa was licensed in United States and Europe for the treatment of anemia with CKD with or without dialysis.

The recommended starting dose (approved by NKF-K/DOQI and FDA) of Epoetin-alfa is 50-100 IU/kg SC or IV thrice weekly. The dose is adjusted ideally to keep the rate of hemoglobin

increase between 1-2 gm/dl/month just to prevent hemoconcentration specially in dialysed patients.[19]

Derbepoetin-alfa

This is second generation erythropoiesis stimulating agent (ESA) containing 2 amino acid substitutions, which provides greater metabolic stability in vivo and increases the elimination half life.

The recommended dose (approved by NKF-K/DOQI and FDA) is weekly injection, starting with 0.45 mcg/kg to increase it upto 1.5 mcg/kg. Some patients may need as once in 2 weeks.[20]

MONITORING TREATMENT OF ANEMIA IN CKD

Monitoring Fe Status

Includes checking TIBC, Serum Ferritin and transferrin saturation. The routine monitoring of Fe store should be at an interval of 4 weeks to 3 months. The value of each parameter is kept above the cut off levels mentioned earlier.[7,8]

Monitoring ESA Response

An adequate Hb response can be expected within 4 to 6 weeks in about 70% of the patients treated with ESA. If the patient's Hb does not rise after 2 months at a dose of 300 IU/kg/wk SC or 450 IU/kg/wk IV or in case of derbepoetin alfa, 1.5 mcg/kg/wk, then it is said to be inadequate response. The causes of inadequate response include Fe deficiency, infection/inflammation, chronic blood loss, aluminium toxicity and PRCA.[18-20]

Monitoring Hemoglobin Level

Anemia in CKD patients, treatment should maintain stable Hb level between 10.5 gm/dl to 12.5 gm/dl. Hb should be checked every 2-4 weeks in the induction phase of ESA therapy and every 1-3 months in the maintenance phase of ESA therapy and Fe deficiency.[18]

NEWER THERAPIES

Despite the successes of epoetin alfa and derbepoetin alfa, the management of anaemia in CKD is poised for further clinical advancement. Several new anemia therapies are in various stages of development. The agent closest to the market is the third generation erythropoiesis stimulating agent-continuous erythropoiesis receptor activator (CERA). Phase 3 clinical testing of CERA has recently been completed. The hypothesis being tested is that CERA administered every 3 to 4 weeks is safe and effective for the treatment of anemia associated with CKD (including patients on dialysis and not on dialysis). CERA's long duration of action is attributed to the addition of a large polymer chain into the erythropoietin molecule. The elimination half life of CERA is approximately 130 hours.[18,21]

Also in the development stages for the treatment of anemia in CKD are the erythropoietin mimetic peptides. One agent in this class, hematide, is in the phase 2 of clinical development. In vitro studies have shown that hematide binds the erythropoietin receptor, triggers intracellular signaling, and causes cell proliferation and differentiation. In vivo, studies have shown that hematide is well tolerated and stimulates erythropoiesis in multiple species to produce a sustained increase in hemoglobin level.[21]

The first oral therapy for the treatment of anemia in CKD is also in phase 2 of clinical development. This oral agent is a hypoxic inducible factor (HIF) stabilizer. It is a possibility that

the HIF stabilizer may surpass the effectiveness of recombinant erythropoietin because of its ability to stimulate iron absorption and suppress the negative effects of proinflammatory cytokines on red blood cell production.[21]

CONCLUSION

To summarize, anemia occurs early in CKD. Anemia can begin in some people who have a GFR as high as 60 ml/min/1.73 m^2. Yet, only a minority of patients who have CKD and anemia ever receive a single dose of an ESA before their kidney function declines enough to require dialysis. CKD is a cardiovascular risk factor and it is very important not to wait for a patient to be on dialysis before treating anemia although that is so often the scenario. A huge potential for making a positive impact exists for the 8 million CKD patients at stage III and higher who are not yet requiring dialysis but who have significant anemia.

Diagnosis of CKD associated anemia involves recognition of a GFR 60 ml/min/ 1.73 m^2 with no other evident cause of anemia in this population. Both currently approved ESAs – Epoetin alfa and derbepoetin alfa – can very effectively treat the anemia of kidney disease. In fact, it is much easier to treat anemia than to treat hypertension, which is another significant cardiovascular risk factor commonly present in this population. Adequate iron level is essential for the correction of anemia by the use of ESAs. The availability of extended dosing regimen in anemic patients with CKD may actually reduce resource utilization and potentially improve compliance, which may benefit older patients in the community and long term care settings. While not currently proven in randomized control prospective trials, early recognition and correction of anemia in patient with CKD may play an important role in ultimately improving outcomes and delaying progression to end stage renal disease.

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Multiple Choice Questions

1. **Chronic kidney disease is defined (as NKF) when the glomerular filtration rate is:**
   A. < 90 ml/min/1.73 m^2
   B. < 60 ml/min/1.73 m^2
   C. < 30 ml/min/1.73 m^2
   D. < 15 ml/min/1.73 m^2
2. **The WHO defines anemia in pregnant woman in CKD when the Hb is:**
   A. < 13 gm/dl
   B. < 12 gm/dl
   C. < 11 gm/dl
   D. < 10 gm/dl
3. **The iron deficiency anaemia is diagnosed in stage 5 chronic kidney disease, when:**
   A. Serum ferritin is < 150 mcg/liter
   B. Serum ferritin is < 100 mcg/liter
   C. Serum ferritin is < 50 mcg/liter
   D. Serum ferritin is < 30 mcg/liter
4. **Regarding treatment of Chronic kidney disease with erythropoietin which one is correct?**
   A. Measurement of erythropoietin is necessary before institution
   B. Only subcutaneous route is given
   C. The recommended starting dose 50-100 IU/kg
   D. Side effect often comples the clinicians to stop its use
5. **Resistance to erythropoietin in CKD is said when:**
   A. A dose exceeds 100 IU/kg/week SC
   B. A dose exceeds 150 IU/kg/week SC
   C. A dose exceeds 200 IU/kg/week SC
   D. A dose exceeds 250 IU/kg/week SC
   E. A dose exceeds 300 IU/kg/week SC
6. **Newer therapeutics in CKD which are under trials are:**
   A. Continuous erythropoietin recetor activator
   B. Erythropoietin mimetic peptides
   C. Hypoxic inducible factor stabilizer
   D. All of the above
   E. None of the above

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1. B 2. C 3. D 4. C 5. E 6. D