Chapter

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Anemia of Chronic Kidney Disease

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Anemia is well known and major complication of chronic kidney disease (CKD) and is considered a hall mark of chronicity of renal disease[1]. Anemia is predominantly due to decreased production of erythropoietin (EPO) by the diseased kidney resulting in reduced production of red cells from the erythroid marrow. EPO is predominantly produced by peritubular cells in the kidney and is the hormone responsible for maintaining the proliferation and differentiation of erythroid progenitor cells in the bone marrow. Loss of peritubular cells leads to an inappropriately low level of circulating EPO in the face of anemia. Besides this, several other factors may contribute to development of anemia in patients with CKD (Table 1).

Table 1: Contributory factors to anemia of CRF

1. Decreased EPO production from the kidneys	7. Hyperparathyroidism
2. Iron deficiency	8. Hypothyroidism
3. Aluminium toxicity	9. Chronic inflammatory states
4. Folate deficiency/ B_{12} deficiency	10. Uremic toxins
5. Reduced RBC survival	11. Occult blood loss (GIT)
6. Hemoglobinopathies	

In addition to erythropoietin deficiency in CKD, iron deficiency is common in patients of CKD and 23-37.5% of patients are deficient in iron and it is a major contributing factor for anemia in these patients. Severity of anemia depends upon severity of chronic renal failure.

Anemia is responsible for many signs and symptoms observed in CKD. It causes marked fatigue and reduced exercise tolerance. Anemia results in left ventricular hypertrophy, angina and heart failure[2]. It also causes impaired immune response, decreased cognitive function, mental ability and disturbed sleep[3]. In addition, anemia may play a role in growth retardation in pediatric patients.

Effects of Correction of Anemia

Improvement in anemia results in improved quality of life, maximal exercise capacity, cognitive function, sleep pattern, nutritional status, improvement of sexual function and immune response (Table 2). It also causes reduction in left ventricular hypertrophy.

Table 2: Beneficial effects of treatment of anemia with rHuEPO

1. Improved health related quality of life	5. Improved hemostatic defect of uremia
2. Improved cognition	6. Reduced cardiovascular complications
3. Improved sexual functions	7. Regression of LVH
4. Enhanced immune response	8. Reduced mortality

Evaluation for Anemia

The current recommendation as defined by anemia working group[4] (National Kidney foundation-DOQl) for target hematocrit/hemoglobin in chronic renal failure patients are hematocrit between 33-36% and hemoglobin between 11-12 gm/dl with appropriate therapy. The availability of recombinant human erythropoietin (rHuEPO) has revolutionized the management of anemia in chronic renal failure. Evaluation of anemia of CRF should be initiated when Hct is <33% (hemoglobin <11 g/dl) in pre-menopausal females and pre-pubertal males and Hct is <37% (hemoglobin <12 g/dl) in post-menopausal females and adult males.

Management of Anemia of CRF

The management strategies for anemia of CRF include:

1. Erythropoiesis stimulating agents
2. Iron status management
3. Miscellaneous drug therapy

Erythropoietin Therapy

The availability of recombinant human erythropoietin (rHuEPO) in 1985 was a significant advance in management of anemia. It is given by subcutaneous route, in the dose of 80-150 IU/kg per week in two to three divided doses. The main advantage of s.c. EPO over i.v. EPO is that for attaining similar rise of Hct, dose requirement is 20 to 40% lower. The response to treatment is seen by a rise in Hct. If the rise of the Hct is by 1% over first week, or more than 8% over 2 weeks after starting EPO dose, it indicates a good response. EPO should be continued till target Hct is achieved. Monitor the Hct every 4 weekly thereafter. Alternatively Darbepoietin-α can be used in place of rHuEPO which has a longer half life and is administered less frequently. It is as effective as EPO in maintaining hemoglobin levels. In addition it assures better compliance, though it is much more expensive. It is not yet available in India.

Many patients achieve target hemoglobin but some patients do not achieve satisfactory response to EPO. The causes of hyporesponsiveness are listed in Table 3. Some patients need adjustment of anti-hypertensive medication as EPO causes a increase in blood pressure.

Table 3: Causes of hyporesponsiveness to EPO

- Chronic Infections/Inflammatory conditions-TB, SLE, AIDS
- Chronic blood loss
- Hyperparathyroidism
- Aluminium toxicity
- Malnutrition
- Underdialysis
- Folate/vitamin B_{12} deficiency
- Hemoglobinopathies
- Hemolysis
- Multiple myeloma
- ACEI therapy

Iron Therapy

The initiation of EPO therapy by increasing erythropoiesis increases the demand of iron and iron deficiency results, because it cannot be met by body iron stores or sometimes even after oral iron supplementation. Iron deficiency can be functional or absolute iron deficiency. Functional iron deficiency can be defined as serum ferritin level >100 µg/l and transferrin saturation <20%. On the other hand, absolute iron deficiency can be defined as serum ferritin level <100 µg/l and transferrin saturation <20%.

Disturbances in iron homeostasis in CKD can be due to number of causes as shown in Table 4 and the diagnosis of iron deficiency in a patient of CKD can be assessed by various indicators of iron status (Table 5).

Table 4: Disturbances in iron homeostasis in CRF

- Reduced Iron absorption from the gut
- Reduced food intake due to anorexia, nausea.
- Reduced intake of iron rich food to cut down protein intake (e.g. meat)
- Inhibition of iron absorption by calcium containing binders, antacids.
- Increased iron losses (GIT, HD etc.)
- Increased IL-1α, IL-6,TNF α resulting in defective iron release.
- Infections and chronic inflammation

Table 5: Indicators of body iron status

1. Serum iron
2. TIBC
3. Serum ferritin
4. % transferrin saturation
5. Serum soluble transferrin receptor assay
6. % Hypochromic RBCs
7. Reticulocyte hemoglobin content
8. RBC-Zinc protoporphyrin
9. Bone marrow examination for iron stores

Treatment of iron deficiency in patients of CKD

Iron therapy could be given as oral iron preparation or as intravenous iron supplements. Patients who do not tolerate oral iron therapy need parenteral therapy. The treatment is given till the patient achieves the target hemoglobin level. Parenteral iron therapy is necessary in patients of CKD on maintenance hemodialysis. Intravenous iron is now known to be better than oral iron in replenishing body iron stores. With intravenous iron, greater hematocrit can be achieved as compared to oral iron and the dose of EPO can be decreased. Usual adult dose is 100 mg intravenously 1-3 times/week to a total dose of 1000 mg in 10 doses. It can be repeated if needed. Slow IV injection into dialysis line at a rate of 1 ml undiluted solution per minute not exceeding 100 mg iron/injection can be given. Iron can also be given as drip infusion for hemodialysis patients by diluting in 100 ml 0.9% NaCl inj. The diluted solution should be infused at a rate of 100 mg of iron over a period of at least 15 minutes. Maintenance dose is 50 to 100 mg every 1 to 2 weeks. Various types of parenteral iron preparations are available such as iron dextran, iron sucrose and sodium ferric gluconate.

Monitoring of the patients of anemia in CKD during therapy:

In people with anemia of CKD, hemoglobin and Hct should be monitored every 2–4 weeks during the initial phase and every 1–3 months subsequently. Besides this, periodic evaluation of iron indices should be done.

Miscellaneous Treatment

Some patients do not respond to EPO and iron therapy. Various factors responsible for this hyporesponsiveness to EPO or Iron therapy have been listed in Table 3. Efforts should be made to correct the underlying defect. Sometimes, these patients may benefit from treatment with various adjuvants which include androgen, folic acid, L-carnitine ascorbic acid, vitamin D, Vitamin B_6. If patient still continues to be anemic, blood transfusion may be required.

a. **Androgens** may be prescribed for anemic patients who cannot afford EPO. Nandrolone decanoate is usually preferred. Prolonged therapy with this agent may be associated with various side effects, thus limiting its use.

b. **L-carnitine**: Used in patients who were hyporesponsive to erythropoietin in the dose of 1-3 mg/kg intravenously. Vesela et al (2001) in their recent study reported a decreased in EPO dose by 37% in patients receiving L-carnitine 1 gm IV post-hemodialysis; during the same time hematocrit increased from 27 to 33%.

c. **Others**: Ascorbic acid 300-500 mg/day is used for patients of haemodialysis. Vitamin E is helpful in reducing EPO doses. Zinc supplementation may be useful in malnourished patients. Growth hormone has been found to stimulate erythropoiesis.

d. **Role of blood transfusions**: In some patients there is a role of blood transfusion. These are severely anaemic patients with haemoglobin less than 5g/dl and hyporesponsive to EPO therapy with chronic blood loss.

SUMMARY

Anemia is a universal feature in patients of chronic kidney disease and contributes significantly to morbidity and mortality in these patients. Anaemia increases with the severity of chronic kidney disease. A large number of Indian patients are already iron deficient prior to developing CKD. With the availability of rHuEPO, large number of patients of CKD with anaemia can be benefitted. rHuEPO and Iron replacement therapy are the mainstay of the treatment of anaemia of CKD. Correction of anaemia in CKD significantly improves the quality of life and decreases cardiovascular morbidity and mortality.

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