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Erythropoietin Resistance In Patients Undergoing Dialysis

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Abstract
Anemia is a very common clinical problem in patients with chronic kidney disease and it is associated with more hospitalizations,increased morbidity and mortality and decreased quality of life in patients undergoing dialysis.
Anemia in CKD is usually normocytic and normochromic. Although CKD and EPO deficiency are strongly correlated, if other causes of anemia are present, therapy with recombinant human erythropoietin (rHuEPO) alone will likely not correct it and this is the concern which defines erythropoietin resistance.
A significant number of patients do not respond to the treatment with recombinant human erythropoietin. The main cause of hyporesponsiveness in these patients is iron deficiency. However, there are other causes of resistance: inflammation, acute or chronic infection, malnutrition, inadequate dialysis, severe hyperparathyroidism and aluminum toxicity. Dialysis modality and biocompatibility of dialysis membranes can also interfere.
Keywords: *Chronic kidney disease, Dialysis, Recombinant human erythropoietin, Iron*

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I. Introduction

Anemia is a very common clinical problem in patients with chronic kidney disease and it is associated with more hospitalizations,increased morbidity and mortality and decreased quality of life in dialysis patients (Kliger et al 2012; Horl 2013).

The main production of erythropoietin (EPO) in adults occurs in the kidney. In CKD patients, the deficiency of EPO disrupts the maturation of erythrocytes from progenitor cells and decreases their survival, thereby resulting in anemia.

Anemia in CKD is usually normocytic and normochromic. Although CKD and EPO deficiency are strongly correlated, if other causes of anemia are present, therapy with rHuEPO alone will likely not correct it and this is the concern which defines erythropoietin resistance.

The erythropoietin resistance index (ERI) is defined as the weekly weight-adjusted αEPO dose (U/kg/week) divided by the hemoglobin level (g/dL) and it is calculated monthly to investigate resistance to αEPO treatment (Santos et al 2018).

Causes of erythropoietin resistance in patients undergoing dialysis

The primary cause of erythropoietin hyporesponsiveness in patients with CKD receiving hemodialysis is iron deficiency. However, even after adequate iron supplementation some patients remain anemic. (Kanbay et al 2010). Other causes of resistance are: concomitant inflammation, acute or chronic infection, malnutrition, inadequate dialysis, severe hyperparathyroidism, aluminum toxicity, cancer, hemolysis, vitamin B12 and folate deficiencies, pure red cell aplasia, and myelosuppressive agents. Dialysis modality and biocompatibility of dialysis membranes can also interfere.

Iron deficiency

Iron deficiency is the most commonreasonfor erythropoietin resistancein CKD and dialysis patients.

The absolute iron deficiency can occur as a result of nutritional deficiency, blood loss from gastrointestinal hemorrhage, and premature destruction (hemolysis) of red blood cells during the dialysis procedure. The erythropoiesis is the largest consumer of iron in the body.

In patients with CKD, absolute iron deficiency is defined as serum ferritin <100 ng/mL (<200 ng/mLfor hemodialysis patients) and/or a transferrin saturation <20%. Functional iron deficiency is characterized with adequate iron stores where iron is not adequately mobilized from the reticuloendothelial system (RES) to support the process of erythropoiesis. Functional iron deficiency anemia is usually successfully treated with intravenous iron infusions (Coyne et al 2007). In contrast, patients with reticuloendothelial blockage do not respond to iron infusions. This condition often occurs during acute or chronic

inflammation/infection. A high erythrocyte sedimentation rate and/or a high CRP level are often observed as well. Typically the serum ferritin level is >200 ng/mL but the transferrin saturation is <20% in both of these conditions.

Microcytosis and hypochromia are very typical foriron deficiency anemia. The biochemical markers of iron deficiency (serum iron, total iron binding capacity, transferrin saturation, serum ferritin, soluble transferrin receptor – sTfR) are of limited value because they vary in several clinical conditions (Brugnara et al 2003). A more sensitive marker of iron deficiency in patients receiving ESA is Reticulocyte Hb Content (CHr).CHr may alsobe an early indicator of the effectiveness of iron replacement therapy.

Hepcidin,a small peptide produced mainly in hepatocytes,inhibits the absorption of iron in the intestines and the release of iron from the reticuloendothelial system. Hepcidin binds to ferroportin, an iron transporter. Decreased serum hepcidin concentrations cause ferroportin molecules to be exposed on the plasmatic membrane and that causes iron to be released. Increased hepcidin levels result in hepcidin binding to ferroportin, which initiates its decomposition. Ultimately, this results in lowered release of iron (Nemeth et al 2004, De Domenico et al 2007).

Malnutrition

Malnutrition can also lead to erythropoietin resistance in patients undergoing dialysis. The main causes of protein energy malnutrition include inflammation, low nutrients intake, insulin resistance, increased protein catabolism and decreased protein synthesis resulting in muscle loss, loss of nutrients and oxidative stress (Avesani et al 2006). Laboratory tests would show low levels of albumin and transferrin saturation index, but high concentration of CRP (Locatelli et al 2006; Kalantar-Zadeh et al 2009) and ferritin (Gaweda et al 2010). The deficiency of vitamin B12 and folic acid can also be associated with anemia and erythropoietin resistance. Moreover, their insufficiency increase homocysteine levels, which result in increased risk of cardiovascular complications in CKD patients (Vecchi et al 2000).

Hyperparathyreoidism

There are several potential mechanisms for hyporesponsiveness to recombinant human erythropoietin in dialysis patients with secondary hyperparathyreoidism: direct toxic effect of parathyroid hormone on the synthesis of erythropoietin, and indirect effect via the induction of marrow fibrosis (Drüeke 1995).

Inflammation

Cytokines related to inflammation (IL-1, IL-6, IFN-γ; TNF-α) can lead to erythroid progenitor cell resistance. They can also damage the delivery of stored iron in the RES which is needed for synthesis of hemoglobin(Cançado et al 2002, Macdougall 2002). Cytomegalovirus infection increases the synthesis of IFN and TNF which can also cause anemia. (Betjes et al 2008). Human parvovirus B19 can induce lysis of erythroid precursors in the bone marrow. (Chisaka et al 2003). Dialysis patients have increased erythrocite destruction and this can worsen the B19 infection. Inflammation increases serum levels of hepcidin. IL-6 induces the synthesis of hepcidin by hypoferremia

Dialysis adequacy

The presence of uremic toxins in patients with CKD inhibits the production of EPO and erythropoiesis. The inadequacy of dialysis is an important cause of anemia in patients undergoing dialysis.
If the appointed dialysis dose is appropriate, it should lead to cost-effectiveness, as patients with the best Kt/V values require lower doses of rHuEPO. (Gaweda et al 2010). Dialysis modality and biocompatibility of dialysis membranes are also to be considered when choosing the adequate treatment for each patient.

Anti-erythropoietin antibodies

Anemia in CKD patients usually is treated by rHuEPO. A small percent of patients synthesize antibodies that can counteract endogenous and recombinant erythropoietin. In most of the cases antibodies are against subcutaneously administerd epoetin alfa. (Macdougall et al 2012). The production of anti-EPO antibodies can lead to development of pure red cell aplasia and transfusion-dependent anemia (Behler et al 2009). Diagnostic confirmation of anti-EPO antibody-mediated PRCA includes detection of antibodies and bone marrow biopsy. If confirmed, erythropoietin administration should be discontinued and the patient should be treated with blood transfusions.

Angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers

Angiotensin II is known to enhance the secretion of EPO, which results in increased erythrocyte mass. It also stimulates the erythroid progenitors proliferation in the bone marrow (Vlahakos et al 2010).

Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) can lead to anemia in CKD patients. The renin–angiotensin system has an important role in hematopoiesis.The angiotensin-

converting enzyme (ACE) is responsible for the decomposition of the tetrapeptide acetyl-seryl-aspartyl-lysyl-proline (AcSDKP).

The blockage of ACE with ACE inhibitors increasesthe circulating levels of AcSDKP and keeps the hematopoietic stem cells in phase G0 of the cell cycle. (Rieger et al 1993). ACE inhibitors increasethe concentrations of AcSDKP in plasma and this may result in resistance to treatment with rHuEPO (Meur et al 2001).

The EPO receptor

Endogenous and recombinant EPO bind to the EpoR receptor and stimulate erythropoiesis(Ng 2003).High levels of soluble form of the receptor (sEpoR) may be associated with needs of higher doses of rHuEPO(Inrig et al, 2011,Khankin et al, 2010) sincethe sEpoR has a higher affinity for EPO and acts as an antagonist of the hormone.That can lead to hyporesponsiveness to recombinant human erythropoietin.

II. Conclusion

Anemia is a very common clinical problem in patients with chronic kidney disease and it is associated with more hospitalizations and blood transfusions, increased morbidity and mortality and decreased quality of life in patients undergoing dialysis.

The treatment of anemia with recombinant human erythropoietin (rHuEPO) in patients with CKD has a major role in the reduction of these complications and improving patient outcomes. The primary cause of hyporesponsiveness to recombinant human erythropoietin in patients with CKD receiving hemodialysis is iron deficiency. However, even after adequate iron supplementation some patients remain anemic. There are other causes of resistance: concomitant inflammation, acute or chronic infection, malnutrition, inadequate dialysis, severe hyperparathyroidism, aluminium toxicity, cancer, hemolysis, vitamin B12 and folate deficiencies, pure red cell aplasia, myelosuppressive agents, genetic polymorphisms, using of ACE-inhibitors and angiotensin II type 1 receptor blockers. Dialysis modality and biocompatibility of dialysis membranes can also interfere. Monitoring of the patients undergoing dialysis through simple blood tests, correcting the anemia and early detection of causes of erythropoietin resistance are the main factors for improving the quality of life in CKD patients.

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