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Update article

Resistance of dialyzed patients to erythropoietin

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ABSTRACT

Resistance to recombinant human erythropoietin is a common condition in dialyzed patients with chronic kidney disease and is associated with more hospitalizations, increased mortality and frequent blood transfusions. The main cause of hyporesponsiveness to recombinant human erythropoietin in these patients is iron deficiency. However, a high proportion of patients does not respond to treatment, even to the use of intravenous iron, which indicates the presence of other important causes of resistance. In addition to the iron deficiency, the most common causes of resistance include inflammation, infection, malnutrition, inadequate dialysis, and hyperparathyroidism, although other factors may be associated. In the presence of adequate iron stores, other causes should be investigated and treated appropriately.

Introduction

Chronic kidney disease (CKD) is considered a public health problem worldwide with high incidence and prevalence rates.[1] In end-stage renal disease (ESRD), renal function must be replaced by dialysis or renal transplantation.[2] In Brazil, the number of patients on dialysis has increased gradually over the years. According to the Sociedade Brasileira de Nefrologia (SBN), 42,695 and 100,397 patients were under dialysis in 2000 and 2013, respectively.[3]

Anemia is one of the most frequent early complications of CKD.[4] The main cause is erythropoietin (EPO) deficiency due to impaired kidney function. However, other causes should be considered when the severity of anemia is inconsistent with the decrease in renal function; when there is evidence of iron deficiency or matching decreases in hemoglobin, leukopenia and/or thrombocytopenia are also found.[5]

The treatment of anemia in CKD patients usually involves the use of recombinant human erythropoietin (rHuEPO). The main cause of rHuEPO treatment failure is the loss or low iron availability.[6] The prevalence of iron deficiency is very common in CKD, affecting as many as 50% of patients.[7] However, despite rHuEPO and intravenous iron in the majority of patients, the prevalence of anemia reaches 34% in Brazil.[8] This indicates the existence of other important factors related to rHuEPO resistance.

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Table 1 – Definition of anemia and hemoglobin target in CKD patients.

	EBPG 2004	NKF/KDOQI 2006/2007	ERBP: anemia group position 2008	KDIGO 2012
Definition of anemia				
Females	<11.5 g/dL	<12 g/dL	<12 g/dL	<12.0 g/dL
Males	<13.5 g/dL <12 g/dL aged >70 years	<13.5 g/dL	<13.5 g/dL	<13.0 g/dL
Hemoglobin target	>11 g/dL >14 g/dL not desirable (>12 g/dL not desirable in CVD)	Generally 11–12 g/dL, not to exceed 13 g/dL	Generally 11–12 g/dL, not to exceed 13 g/dL	Generally ≤11.5 g/dL, not to exceed 13 g/dL

EBPG: European Best Practice Guidelines; NKF/KDOQI: National Kidney Foundation Kidney Disease Outcomes Quality Initiative; ERBP: European Renal Best Practice; Kidney Disease: KDIGO: Improving Global Outcome; CVD: cardiovascular disease.

The definition of anemia in CKD patients has changed with some guidelines being produced over the last few years. In 2004 the Revised European Best Practice Guidelines (EBPG) on Anemia defined low hemoglobin levels as values <11.5 g/dL in adult females and <13.5 g/dL in adult males (<12 g/dL in over 70-year olds). Patients with CKD should maintain a hemoglobin level >11 g/dL (hematocrit >33%). In addition, levels >12 g/dL are not recommended for patients with severe cardiovascular disease.[9]

An update of the 2006 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) guidelines in 2007 suggested that anemia is associated with hemoglobin levels <13.5 g/dL in adult males and <12.0 g/dL in adult females. In patients with CKD, hemoglobin should be between 11 and 12 g/dL, however hemoglobin targets greater than 13 g/dL may increase the risk for serious adverse effects and are not recommended.[5,10]

The KDOQI modified the EBPG definition defining anemia in adult males as hemoglobin <13.5 g/dL regardless of age since the decrease in hemoglobin levels among over 60-year-old males is frequently related to concurrent diseases. In addition, in adult females the hemoglobin target is 12 g/dL. The European Renal Best Practice (ERBP) Work Group agrees with the KDOQI definitions.[11]

Recently, the Kidney Disease: Improving Global Outcome (KDIGO) group defined anemia in adults and children aged >15 years with CKD when the hemoglobin levels are <13.0 g/dL in males and <12.0 g/dL in females.[12] Table 1 shows the definitions of anemia and hemoglobin targets in CKD patients.

Although there is no consensus about the definition for rHuEPO resistance, the evaluation of resistance is recommended if there is an increase ≥25% in erythropoietin dose or <1 mg/dL gain in hemoglobin levels after 2–4 weeks of treatment.[13]

According to the Brazilian Ministry of Health,[14] rHuEPO resistance is defined as a persistent anemia (hemoglobin <10–12 g/dL) or the necessity of very high erythropoietin doses of epoetin alfa (300 IU/kg/week subcutaneously or 450 IU/kg/week intravenously). Epoetin alfa should be initiated at a dose of 50–100 IU/kg subcutaneously, one to three times a week. The initial goal of treatment is to achieve a rate of weekly increase in hemoglobin levels of 0.3 g/dL. If after four weeks of treatment, this response is not observed and the hemoglobin remains below 11 g/dL, the dose should be increased by 25%. However, after four weeks if the hemoglobin level is greater than 13 g/dL, the drug should be suspended temporarily, since the maintenance of higher hemoglobin levels is associated with increased morbidity and mortality. The recommended therapeutic target is to preserve hemoglobin levels from 11 to 12 g/dL or hematocrit from 33% to 36%.[5]

Anemia in CKD is usually normocytic and normochromic. The characteristics of erythrocytes as determined by hematimetric indices, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) can characterize the etiology of anemia.[15] In addition to hematimetric indices, the laboratory investigation includes complete blood cell count, reticulocyte count, serum iron, determination of the transferrin saturation and serum ferritin, as well as occult blood in stools and the levels of folic acid and vitamin B12.[12,16]

The biochemical markers of iron deficiency (serum iron, ferritin, transferrin saturation and soluble transferrin receptor – sTfR) have limited value in functional iron deficiency as they are changed in several clinical conditions such as the ones that evolve with rHuEPO therapy.[17] However, reticulocyte hemoglobin content (CHr or Ret-He) is a sensitive indirect marker of iron deficiency, which reflects recent changes in erythropoiesis.[18] The measurement of CHr in peripheral blood samples is useful for assessing the amount of functional iron that was available in the bone marrow for new red blood cell production over the previous 3–4 days.[19] CHr may be a more sensitive marker of functional iron deficiency in patients receiving erythropoietin therapy.[20] It may also be an early indicator of the effectiveness of iron replacement therapy.[21]

Thomas and Thomas[22] presented a novel approach to functional iron deficiency with the use of CHr and the percentage of hypochromic erythrocytes (HYPO). Functional iron deficiency was defined as a CHr <28 pg and a HYPO <5% based on the levels in healthy controls. Moreover, the sTfR-F index (sTfR/log ferritin), which reflects the iron store status, can be used to differentiate functional iron deficiency in states of iron depletion and iron repletion. A diagnostic strategy combined CHr and sTfR-F index to identify four major categories of iron deficiency: (1) iron repletion with normal erythropoiesis (CHr and