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Optimizing Anemia Management in Chronic Kidney Disease 5 Dialysis Patients

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Anemia is a complication of chronic kidney disease (CKD) that occurs usually when glomerular filtration rate (GFR) decline below 40 ml/min (stage 3). Blood hemoglobin concentration (Hb), the conventional marker of anemia, may start declining earlier in diabetic patients and later in polycystic kidney disease patients. Renal anemia is a disabling complication that contributes to deterioration of quality of life and exacerbation of functional symptoms in CKD patients. By altering physical and mental component scores renal anemia reduces significantly the quality of life of dialysis patient, enhances burden of chronic disease and exacerbates uremic symptomatology. Several clinical studies have clearly indicated that low hemoglobin concentration amplifies the cardiovascular symptomatology, potentiates the pathogenic role of uremic-related factors implicated in accelerated atherosclerosis and aggravates negative metabolic impact of uremic manifestations (malnutrition, immunodeficiency, sexual dysfunction, cognitive dysfunction…). In addition, renal anemia is a severe comorbid condition that induces organs lesions directly via chronic tissue hypoxia or indirectly via compensatory mediated mechanisms (HIF), and may contribute to precipitate adverse cardiovascular events.

Correction of anemia in dialysis patients represents today, a major goal of treatment adequacy to reduce the functional symptomatology and alleviate partially burden of CKD and treatment dependency. Over the last 20 years, erythropoietic stimulating agents (ESA) and intravenous iron compounds have revolutionized the management of anemia in CKD dialysis patients. In the majority of cases, the correction of anemia is achieved easily contributing to a significant improvement of the life of dialysis patients and also by reducing this handicapped situation. Anemia management in dialysis patients has been refined over time and hemoglobin targets have been adjusted according to major interventional studies' outcome. Based on initial encouraging results obtained with partial correction of anemia (Hb 10-12 g/dL) some clinical trials have attempted to achieve a complete correction of anemia (Hb 12-14 g/dL) in selected CKD populations (e.g., cardiac, diabetic). Unfortunately, safety issues have been raised by outcome of these trials leading to revised best practices guidelines and anemia correction targets. Nowadays, it is strongly recommended to achieve only a partial correction of hemoglobin concentrations. Hemoglobin variability over time (e.g., Hb cycling) is a clinical feature that has been reported recently adding a potential deleterious factor to morbidity and mortality of CKD hemodialysis patients. Effects of Hb cycling on morbidity and mortality of CKD patients are still matter of debate, since this phenomenon remains based on observational studies and causality relationship is difficult to ascertain. Recent studies tend to prove that Hb cycling reflects more instability of CKD patient (occurrence of intercurrent events) and/or ways of managing the anemia (protocol, algorithm, physician practices, type of ESA) than being a risk marker. However, working on and preventing large hemoglobin fluctuation is now clearly recommended by international guidelines to reduce additional cardiovascular insults. In addition, resistance to ESA action has been recently identified as being a major risk factor in hemodialysis patients. Whatever reasons of ESA resistance are (inflammation, infection, intercurrent disease and/or event…), hyporesponsiveness to ESA is a strong indicator of severity and poor prognosis in dialysis patients. ESA resistance needs to be explored in a systematic way and to be treated accordingly.

Optimizing anemia management in dialysis patients has thus become a rather complex and challenging situation for nephrologists. Correction of anemia is potentially associated with untoward effects when target hemoglobin levels are not met (suboptimal correction) or, on the contrary, when Hb levels exceed target values (overshoot correction). Apart from this mortality risk, high ESA doses increase tremendously the overall cost of renal replacement therapy. In the particular case of hemodialysis patients, hemoglobin concentrations are strongly influenced by temporary or general patient condition that prevail and change (inflammation, infection, fluid overload, intercurrent disease and/or event, iron depletion…), such conditions being associated to intra-individual dose-response variability. The current availability of different ESAs having various pharmacokinetic and pharmacodynamic profiles (long versus short acting agents, route administration IV versus SC) has created an additional level of complexity in the management of renal anemia. Finally, the extensive use of intravenous iron to overcome ESA drawbacks has exposed dialysis patients to iron overload as attested by high ferritin levels and abnormal liver deposits.

Correction of anemia with ESA and iron administration is an essential component of CKD patient management. Recent KDIGO and ERBP guidelines have clearly stressed benefits and risks of correcting the anemia with ESA. Based on these guidelines, management of anemia in CKD hemodialysis patients follows a precautious stepwise approach consisting in four steps: 1. Diagnose and evaluate anemia in CKD hemodialysis patient including its tolerance; 2. Use preferentially iron to treat anemia in CKD hemodialysis patient; 3. Use of ESAs and other agents to treat anemia in CKD if required by clinical condition and reduce Hb target 10 to 12 g/dl; 4. Red cell transfusion to treat anemia in CKD.

The recommendation is to diagnose and evaluate anemia in CKD HD patient least every 3 months in stable CKD 5HD patients not on ESA therapy and at least monthly intervals in patients treated by ESA. Complete blood count (CBC), including Hb concentration, red cell indices, white blood cell count and differential, and platelet count, absolute reticulocyte count and serum ferritin level and transferrin saturation (TSAT) need to be considered.

Use preferentially iron to treat anemia in CKD hemodialysis patient. For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron if TSAT < 30% and ferritin is <500 mg/L.

Use of ESAs and other agents to treat anemia in CKD for adult should be ideally initiated when hemoglobin is between 9.0-10.0 g/dL, but may be considered being started earlier (Hb >10.0 g/dL) as far as quality of life is concerned or in selected dialysis patients.

It is suggested to maintain Hb concentration between 10.0 and 11.5 g/dL in adult patients. Individualization of therapy target and higher Hb concentration (>11.5 g/dL) may be required in selected hemodialysis patients, based on medical indication but being prepared to accept the documented risks associated with higher Hb levels.

During the initiation and maintenance phases of ESA therapy, Hb levels have to be measured at least monthly.

ESA hyporesponsiveness may be considered when stabilized CKD hemodialysis require 2 increases in ESA doses up to 50% beyond the baseline dose. In these cases, repeated escalations in ESA dose beyond double the baseline dose are not suitable. Acquired ESA hyporesponsiveness need to be explored and treated for specific causes of poor ESA response.

Red cell transfusion to treat anemia in CKD should be avoided to minimize the general risks related to their use. The decision to transfuse a CKD patient with non-acute anemia should be determined by the occurrence of symptoms caused by anemia.

Clinical benefits of optimal anemia management in CKD hemodialysis patients are well established in practices. Anemia correction, combining ESA and IV iron supplementation, is the most clinically evident and patient perceived benefits of the therapy. Maintaining Hb concentration between 11 to 12 g/dL has several benefits: it suppresses blood transfusion needs; it improves physical performances, QOL and corrects malnutrition; it improves cardiac performances. It is also worthwhile, to exclude additional causes of anemia, including blood loss (gut, hemodialyzer, blood sampling), functional

iron deficiency, hemolysis, inflammation or metabolic factors (hyperparathyroidism). Hemodialysis adequacy (dialysis dose) and nutritional status (protein energy wasting, vitamin and nutrient deficiencies) are also significant factors that need to be considered for improving ESA response and anemic correction in hemodialysis patients.

Failure to attain target Hb concentration with adequate ESA dose treatment is associated with an increased risk of mortality and hospitalization. Iron deficiency is the most common cause of ESA resistance that can usually be overcome with IV iron administration. Inflammation is also a quite common cause of ESA resistance that blocks the utilization of iron (functional iron deficiency) and inhibits myeloid erythroid progenitor proliferation. Markers of iron status including transferrin saturation, percent of hypochromic reticulocytes cell (iron availability) and ferritin (total body iron stores) and those of inflammation (CRP) need to be evaluated regularly (monthly to quarterly).

Recognizing the complexity of treating anemia in CHD hemodialysis patients as well as the variability of patient sensitivity, different tools facilitating management of anemia in this context have been tested. Several preliminary studies have underlined the benefits of using prescribing tools and guided protocols to facilitate and to individualize anemia treatment. More sophisticated ESA modeling technics using personal characteristics and accounting for temporal changes in ESA sensibility have confirmed in pilot studies the potential benefits of these approaches. Unfortunately, guidelines are never fully implemented, nor consider or account for physician and/or dialysis facility practice patterns. However, the DOPPS study has clearly shown that such practice features have a determinant impact on anemia outcomes and ESA consumption.

In conclusion this presentation will summarize and provide attendees key elements in a practical way to optimize anemia management in CKD hemodialysis patients while best using ESA and iron supplementation.