Anaemia Management of Children with Chronic Renal Failure

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Introduction

Since the association between kidney disease and anaemia was first described in 1836 /1/, a reduced red cell mass has been considered a characteristic feature of chronic renal failure (CRF). In paediatric patients with CRF a linear relationship between glomerular filtration rate (GFR) and hematocrit (Hct) has been observed /2,3/.

Inadequate erythropoietin production is one of the main causes of renal anaemia. Other causes are: reduced red blood cell lifespan, chronic blood loss, iron deficiency, inhibitors of erythropoiesis and malnutrition. The advent of recombinant human erythopoietin therapy (rHuEPO) in 1986 /4,5/ revolutionized the treatment of anaemia in CRF.

While rHuEPO is effective in the correction of anaemia in most cases, there is a significant number of patients who fail to respond, and there is an extremely low number of those who get pure red cell aplasia (PRCA) during rHuEPO therapy /6/. The optimisation of rhEPO therapy includes the awareness of target Hct and Hb, defining the renal anaemia management period, drug dosage and mode of its application, and the significance of adjuvant therapy. This paper discusses optimal modes of anaemia management in children with CRF.

Evaluating anaemia

The European Best Practice Guidelines (EPBG) /7/ have recommended a work-up for the diagnosis of anaemia in children with CRF whenever: a) the Hb concentration is <11 g/dl (Hct <33%) in pre-pubertal and b) the Hb concentration is <12 g/dl (Hct <37%) in post-pubertal patients.

Evaluation of anaemia in patients with CRF begins with general clinical examination so as to assess its possible causes (chronic blood loss, nutritional deficiencies) and its clinical impact /7/. Basic laboratory evaluation of anaemia should consist of measuring the following: (1) Hb concentration and Hct level, (2) red blood cell indices including mean corpuscular volume (MCV) and mean corpuscular Hb (MCHC), (3) absolute reticulocyte count, (4) iron stores - serum apoferritin concentration (SAF), (5) iron supply for erythropoiesis including transferin saturation (TSAT) or, better when available, the percentage of hypochromic red blood cells (HCRBC) and reticulocyte hemoglobin content (CHr), and (6) C-reactive protein (CRP) as a marker of inflammation. MCV and MCHC are readily available laboratory tests, but do not become diagnostic until moderate-to-severe iron deficiency anaemia is present. Although TSAT and SAF are widely available and are commonly used measures for iron status, these markers of iron stores do not always provide the most reliable or accurate information, especially when isolated determinations are utilized /8,9/. HCRBC has been recently introduced as a sensitive tool in the diagnosis of iron deficiency in dialysed patients, which, however, can be influenced by inflammation. Furthermore, because of the longer life-span of mature erythrocyte, HCRBC fails to provide relevant information on rapid change in iron utilization. With advent of novel automated flow-cytometry technique, measurements of reticulocyte haemoglobin concentration (CHr) allow extremely early and objective information on erythropoetic activity in anaemia. Reticulocyte fluorescence intensity is directly proportional to the quantity of intracellular RNA and thus expresses the function of cellular maturity. The most immature reticulocyte expresses high-fluorescence intensity regions (HFR). Therefore, CHr and HFR have been proposed as surrogate markers of iron status and the early predictors of response to iron therapy with the highest accuracy (sensitivity 96%-100% and specificity of 80-100%) /9,10/.

Target haemoglobin concentrations-tailoring treatment for renal anaemia

Correction of anaemia dramatically improves the life of the child with CRF /11-18/. Presently, the goal of rHuEPO therapy in children is to maintain the Hct at 33% to 36% /7,19,20/. The choice of Hb targets for treating patients with renal anaemia is still a matter of great debate /21/. At the moment, no upper limit has been determined, except for patients with cardiovascular disease, for whom Hb concentration limited to 11-12 g/dl is suggested /7,19,21/. Exact target Hb concentrations >11 g/dl should be tailored for individual patients /21/.

Preliminary data on pre-dialysis patients suggest that anaemia management plays an important role in delaying or halting progression of CRF and its associated co-morbidities, especially cardiovascular ones /18,22,23/. The results of the trials evaluating the benefits of normalizing Hb early in the course of renal disease are eagerly anticipated.

Erythopoetin dosage and mode of application

Sensitivity on biotechnologically produced rHuEPO has been shown to be lower in children and larger dosage must be used compared with adults /12,20, 24, 25/. In predialysed children or after renal transplantation, the starting EPO dose of 25-50 U/kg per week in one to two doses is

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recommended. For dialysed children 50-150 U/kg per week are given in two or three doses with stepwise increase of 50 U/k per week. Haemoglobin should increase at a rate of 1 g/dl per month to the target level and than the maintenance dose is determined individually. Children younger than 5 years of age may require greater doses of rHuEPO on the body weight basis (up to 300 U/kg/week) than older paediatric patients and adults /7,20,24,25/. It may be given subcutaneous or intravenously. The efficacy of rHuEPO is better (15-50%) when given by subcutaneous route due to more favourable pharmacodynamics /20,26 /. If intraperitoneal administration is used, it is best to infuse it into a "dry" abdomen or with a minimal amount of dialysate /27/.

Appropriate administration of rHuEPO, a gradual control of anaemia (weekly rise in Hct should not exceed 1%) and precise monitoring of treatment decrease adverse reactions of rHuEPO. Nowadays a hot topic is erythroblastopenia (PRCA), severe undesired affect of rHuEPO from induced antierythropoietin antibodies /6/. As far as it is known, no case of PRCA has been reported in children. Taking into account that PRCA has appeared only after subcutaneous route of administration, especially of epoetin alpha, the following is recommended: intravenous administration of epoetin alpha and epoetin beta in hemodialysis patients, and subcutaneous administration of epoetin beta in patients with CRF not yet receiving dialysis and peritoneal dialysis patients.

The significance of adjuvant therapy

Iron requirements are increased in patients with CRF due to EPO-facilitated iron utilization, chronic blood loss, decreased iron intake and absorption, and iron sequestration secondary to chronic inflammatory processes. In paediatric HD patients iron losses are estimated at 1.6 g/1.73 m2 BSA /19/. Iron deficiency (absolute or functional) is the most important cause of erythropoietin resistance. It may be prevented by concomitant use of iron supplementation when rHuEPO treatment is prescribed. If adequate iron stores cannot be maintained with oral therapy (2-3, max 6 mg/kg/day), intravenous iron therapy should be instituted. It has been demonstrated that maintenance intravenous iron is more effective and cheaper than intermittent dosing in pediatric hemodialysis patients /28/. For optimal rHuEPO response the goal should be to maintain serum iron in the normal range, SAF 200-500 μg/l (not to be persistently >800 μg/l), TSAT 30-40% (not to be >50%), HCRBC <2.5% and Chr>28 pg /9/. The best erythrocyte and iron metabolism indices are changes in CHr (cut-off value of >1.2 pg) and HFR (cut –of value of >500/μl) at either 2 or 4 weeks during aggressive intravenous iron treatment /10/.

Conclusion

Early treatment of anaemia well before kidney function deteriorates to the point of requiring dialysis is now in the focus of interest. Future research in anaemia management in children with CRF should be concentrated on three major areas: 1/ target hematocrits >36%, 2/ the use of intravenous iron, especially new sucrose based products, and 3/ the long term effects of normalisation of Hct/Hb on the child's development.

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