ANEMIA IN CHRONIC KIDNEY DISEASE (CKD).
DO WE KNOW HOW TO TREAT IT PROPERLY?

NIEDOKRWISTOŚĆ W PRZEWLEKŁEJ CHOROBIE NEREK (PCHN).
CZY WIEMY JAK PRAWIDŁOWO NALEŻY JĄ LECZYĆ?

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Summary
Renal anemia is one of the major complications observed in patients with chronic kidney disease (CKD). It is caused mainly by a relative erythropoietin deficiency due to progressive damage of renal parenchyma. The primary goal of anemia treatment using available today ESAs is not only to improve the quality of life of patients but, above all to reduce cardiovascular mortality. The target hemoglobin concentration during application of ESA in CKD patients treated conservatively and renal replacement therapy patients was and still is being discussed among nephrologists. Based on the clinical trials performed so far, it seems that in patients with renal anemia we should individualise treatment with ESA, seeking partial rather than complete correction of anemia.

Streszczenie
Niedokrwistość nerkopochodna jest jednym z istotnych powikłań obserwowanych u pacjentów z przewlekłą chorobą nerek (PCHN). Jest ona spowodowana głównie względny niedoborem erytropoetyny wskutek postępującego uszkodzenia miąższu nerek. Podstawowym celem leczenia niedokrwistości przy pomocy dostępnych współcześnie czynników stymulujących erytropoację (ESA) jest nie tylko poprawa jakości życia chorych, ale przede wszystkim zmniejszenie śmiertelności sercowo-naczyniowej. Docelowo stężenie hemoglobiny w czasie stosowania ESA u pacjentów z PChN leczonych zachowawczo, jak i dializowanych, było i nadal jest przedmiotem dyskusji w środowisku nefrologicznym. W oparciu o przeprowadzone do tej pory badania kliniczne wydaje się, iż w przypadku chorych z niedokrwistością nerkopochodną należy prowadzić indywidualizację leczenia z zastosowaniem ESA, dając raczej do częściowej niż całkowitej korekcji niedokrwistości.

Key words: renal anemia, chronic kidney disease, iron, hemoglobin, erythropoietin
Słowa kluczowe: niedokrwistość nerkopochodna, przewlekła choroba nerek, żelazo, hemoglobina, erytropoetyna

INTRODUCTION
Anemia is one of the symptoms of chronic kidney disease (CKD) and an important cause of morbidity and cardiovascular mortality. ARIC Study (Atherosclerosis Risk In Communities) showed that the slight increase in serum creatinine levels (> 1.2 mg/dl in women, > 1.5 mg/dl in men) together with anemia occurrence was associated with almost 3-fold risk of coronary artery disease (CAD). A similar relationship
was not observed in patients with elevated creatinine level without accompanying anemia [1]. DOPPS study, which was published in 2004, showed that 1.0g/dl rise (from the baseline) in hemoglobin reduces mortality by 5% [2].

In accordance with the criteria proposed by the WHO we recognize anemia when Hb is less than 13 g/dl in men and postmenopausal women, and less than 12 g/dl in women before menopause. According to the DOQI (Dialysis Outcome Quality Initiative), we deal with anemia when the Hb is about 1 g / dl lower than those defined by WHO [3].

THE PATHOGENESIS OF RENAL ANEMIA

One of the important cause of anemia in CKD is reduced red blood cell production by the bone marrow, caused by deficiency of erythropoietin due to the progressive renal damage. The main site of erythropoietin production in adults are tubular epithelial cells and interstitial fibroblasts at the border of the cortex and outer core of the kidney. Erythropoietin synthesis is regulated in a feedback mechanism, depending on the oxygen partial pressure of blood flowing through the kidney.

Red blood cell survival time in patients in advanced stages of chronic kidney disease is reduced to 1/3 survival time of erythrocytes in healthy individuals. Shorten survival time of erythrocytes is a consequence of accumulation of uremic toxins and erythrocytes damage, as a result of mechanical and osmotic or oxidative stress as well as.

Increased production of reactive oxygen species and impaired efficiency of antioxidant mechanisms in CKD lead to oxidative stress. This leads to increased plasma levels of lipid peroxidation products, protein, carbohydrates, and deoxyribonucleic acid [4]. It is believed that the impairment of the natural antioxidant system in erythrocytes is one of the most important factors increasing lipid peroxidation in erythrocyte membranes. This results in blood cell hemolysis, and therefore, intensification of anemia in patients with CKD [5]. CKD patients present significantly elevated plasma homocysteine level which is responsible for increased LDL oxidation in vascular wall. This results from the cytotoxic effects of homocysteine on the extracellular superoxide dismutase, whose activity decreases in direct proportion to the increase in concentration of homocysteine. In this way the vessel wall is deprived of the physiological antioxidant protection and becomes more susceptible to the harmful effects of reactive oxygen species [6]. Probably, intensification of lipid peroxidation in cellular membranes is one of the factors jointly responsible for the reduction of erythrocyte survival and development of renal anemia.

On the other hand, it should be remembered that patients with CKD are exposed to repeated, frequent loss of blood due to gastrointestinal tract bleeding, frequent blood sampling for laboratory test and hemodialysis procedures itself (blood lose in extracorporeal circuit). It is estimated that during one hemodialysis session blood lose is approximately 20 ml as a result of puncture of arteriovenous fistula and loss of blood in the dialyzer. It gives blood lose of approximately 3 000 ml per year.

Moreover, drugs administration particularly commonly used ACE-I and AT1-blockers may aggravate renal anemia. It is related with deficiency of angiotensin II, which directly stimulates the synthesis of erythropoietin, reduce hypoxia, and is a strong stimulus for EPO production and may inhibit the proliferation of erythroblasts [7]. Thiazide diuretics administration may also (together with ARBs or ACE-I treatment) diminish endogenous production of erythropoietin by reducing oxygen supply as a result of active Na-Cl cotransporter inhibition in distal tubules [8].

Iron deficiency is the most common deficiency in CKD. Absolute iron deficiency in stage 4 - 5 CKD occurs when the transferrin saturation falls below 20% and ferritin levels is below 100 mg/ml [9]. In clinical practice, it is important to distinguish between functional iron deficiency, which corresponds to the treatment, and iron deficiency called ‘inflammation block’. The latter is accompanied by chronic diseases caused by inflammation, and there is no improvement due to iron supplementation in this case.

The main objective of anemia treatment in patients with CKD is to improve quality of life and reduce mortality. It has been shown that the decrease in Hb of 1 g/dl was associated with increased mortality in 14-18% of the population of patients on dialysis, and the concentration of Hb below 8 g/dl resulted in two fold higher risk of death than the level of Hb 10-11 g/dl [10]. In many studies, both retrospective and prospective recommended range of concentrations of Hb was evaluated. Most of the researchers confirmed that the concentration of Hb> 11 g/dl affects better outcomes and and better improvement in quality of life
in both predialysis and renal replacement therapy
care that Hb concentration > 13 g/dl, paradoxically
increases the morbidity and mortality. The target
hemoglobin concentration should depend on clinical
status, age, gender, physical activity, the coexistence of
other factors of cardiovascular disease and dialysis
modality.

CONTROVERSY IN RENAL ANEMIA TREATMENT

The CREATE STUDY and the CHOIR STUDY,
the results of which were published in 2006, were the
first trials to answer the question about hemoglobin
concentration in chronic renal failure patients. Which
therapeutic option is better – partial or complete
correction of hemoglobin level?

In the CREATE Study (Cardiovascular Risk
Reduction by Early Anemia Treatment) 603 patients
with chronic kidney disease (CKD) stage 3 and 4
eGFR range 15 to 35 ml/min per 1.73 m2 of body-
surface area) and mild-to-moderate anemia
(hemoglobin level, 11.0 to 12.5 g per deciliter) were
randomly assigned to a group with a target hemoglobin
value in the normal range (13.0 to 15.0 g per deciliter,
group 1) and to a group with subnormal range (10.5 to
11.5 g per deciliter, group 2). Subcutaneous
erthropoietin (epoetin beta) was initiated at
randomization (group 1) or only after the hemoglobin
level fell below 10.5 g per deciliter (group 2). During
the 3 years observation, in spite of better quality of life
in arm with higher hemoglobin concentration, there
were no differences in left ventricular mass index
between these two groups noted. Complete correction
of anemia did not affect the likelihood of a first
cardiovascular event (58 events in group 1 vs. 47
events in group 2). The mean estimated GFR was 24.9
ml per minute in group 1, and 24.2 ml per minute in
group 2 at baseline, and decreased by 3.6 and 3.1 ml
per minute per year, respectively (P=0.40). Dialysis
was required in more patients in group 1 than in group
2 (127 vs. 111, P=0.03). There were no differences in
total mortality, cardiovascular mortality, hospitalizations rate between group 1 and group 2 [11].
The authors of the trial concluded that in patients with
chronic renal failure, early complete correction of
anemia does not reduce the risk of cardiovascular
events.

The CHOIR study (Correction of Hemoglobin and
Outcomes in Renal Insufficiency) compromised 1432
patients with CKD and Hb level below 11.0 g per
deciliter. Patients were randomly assigned to receive a
dose of epoetin alfa targeted to achieve a hemoglobin
level of 13.5 g per deciliter and other group to receive
a dose targeted to achieve a level of 11.3 g per
deciliter. Early termination of study was performed
after 16 months because patients assigned to high
hemoglobin group (target level 13.5g/dl) showed
higher rate of cardiovascular events (CV death and
hospitalization related to decompensated heart failure.)
[12, 13].

The results of these 2 studies proved that complete
renal anemia correction is not beneficial for CKD
patients and there is no reduction in cardiovascular
mortality and the incidence of new cardiovascular
events in this population. It is worth noticing that
higher morbidity and mortality rate in higher
hemoglobin concentration arm was mainly related to
toxicity of high dose of erythropoetin and intravenous
iron administration but not by hemoglobin
concentration >13.0g/dl itself. It appears that high dose
of erythropoietin may activate RAAS, increase
endothelin-1 (ET-1) production and diminish
tromboxane and prostacycline release in vascular wall.
This may lead to higher blood pressure and higher
cardiovascular events rate [14]. Moreover, high
erthropoietin dose in renal anemia treatment may
contribute to tissue remodeling, intensification of
chronic inflammation via activation of kB nuclei factor
and increase production of many cytokines, growth
factors and procoagulation mediators. This may lead to
profibrogenic action of erythropoietin and other
erthropoietin stimulation agents (ESA). [15].

High doses of ESA and fast correction of anemia
may cause detrimental effects and may contribute to
acceleration of CKD in patients on conservative
treatment with Hb level above 13.0g/dl achieved in a
very short time. On the other hand, in hemodialysis
patients posthemodialysis hemoconcentration in
individuals with Hb level>13.0g/dl may also cause
higher cardiovascular events rate. Therefore, anemia
treatment in this population should be very cautious.

Another worth mentioning study is the TREAT trial
(Trial to Reduce Cardiovascular Events with Aranesp
Therapy) the results of which were published in 2009
[16]. The TREAT was a randomized, double-blind,
placebo-controlled trial conducted at 623 sites in 24
countries. The TREAT trial tested the hypothesis that
the use of ESA would improve outcomes in patients
with diabetes and CKD. 4038 patients with diabetes
and CKD on conservative treatment were enrolled to the study. 2012 patients were randomized to darbepoetin alfa treatment to achieve Hb 13.0g/dl and 2026 to placebo arm. In placebo arm usage of darbepoetin alfa as a 'rescue therapy' was possible in patients with Hb level <9.0g/dl. The primary endpoints in this trial were: time to composite outcome of death from any cause or a CV event (MI, stroke, CHF, hospitalization for myocardial ischemia) and time to ESRD or death. Mean Hb concentration in darbepoetin-alfa arm was 12.5g/dl and in placebo arm it was 10.6g/dl. In this trial there were no statistically significant differences in death of any cause, occurrence of CV events (non fatal myocardial infarction (MI), unstable angina, heart failure, or stroke) and ESRD with dialysis requirements. In darbepoetin-alfa arm there was twofold increase in stroke risk and higher risk of death because of cancer in these patients in whom darbepoetin-alfa was started and there was cancer occurrence at the beginning of treatment with ESA. There was a reduction in the need for packed red blood cell transfusion with darbepoetin alfa, but a higher risk of venous and arterial thromboembolic events, as well as stroke, and a trend toward hypertension with the use of darbepoetin alfa. In placebo group, higher need for iron administration was observed. The authors of TREAT Trial concluded that there is no need for the routine use of ESAs in patients with diabetes and CKD on conservative treatment, and in each of patients commencement of ESA treatment requires awareness of benefits and risks of such decision.

The range of Hb value during anemia treatment is still matter of debate. In the end of 2010 Food and Drug Administration suggested Hb range between 10-12g/dl, NFK-DOQI recommendations from 2007 suggested range between 11-12g/dl. It seems sensible not to exceed the value of 12.0g/dl during the correction or maintain phase of treatment. In spite of a great controversy in anemia treatment with usage of ESAs, such therapy is still valuable for CKD patients but should be individualized and safe in each case [17].

Iron deficiency plays an important role in pathogenesis of renal anemia, (it is the most common cause of hyporesponsiveness to ESAs) and iron status needs monitoring during ESAs administration. Iron plays crucial role not only in erythropoiesis. Free iron activation may cause induction of inflammation, oxidative stress, and kidney damage especially when correction is made by intravenous iron administration.

Iron absorption, transport and storage is regulated by specific protein such as transferin and ferritin. Annual iron loss in hemodialysis patients is approximately 2.0g. Iron deficiency can be easily corrected by intravenous iron administration, which is more effective than oral iron supplementation because of inadequate iron absorption. Correction of iron deficiency may cause rise in hemoglobin level in most patients. There is strong suggestion that high dose of intravenous iron supplementation may accelerate cardiovascular damage and increased risk of bacterial infection. Several recent clinical studies have shown the opposite effects as long as intravenous iron was adequately dosed [18]. According to KDOQI guidelines, ferritin level in hemodialysis patients should be greater than 200mg/dl, but level greater than 500mg/dl is an indication to iron supplementation withdrawal [3]. In the DRIVE study intravenous administration of ferric gluconate was highly efficacious in anemic hemodialysis patients with high serum ferritin level (>800mg/dl) and low transferrin saturation. 12 weeks of ferric gluconate supplementation in patients with ferritin level between 500-1200mg/dl showed significant hemoglobin increase and diminish of ESAs dosage. But limitation of this study was: short time of observation and lack of information about the iron overdosing risk. [19]. In conclusion, we should always be aware of ESAs overdosing/toxicity, iron overdosing and toxicity during anemia treatment. Such awareness facilitates the application of the best management strategy in both ESAs and iron dose titration in correction and maintenance therapy [20]. Commencement of ESAs treatment without iron status correction is appropriate.

In American population based study, Ht range between 33-36% was related with lowest all caused, cardiovascular mortality and hospitalization rate due to infection in compare to Ht range between 30-33% [21]. In Normal Hematocrit Study – prospective study comparing outcomes in 1233 hemodialysis patients with congestive heart failure or ischemic heart disease receiving treatment with epoetin alfa who were randomly assigned to the normal-hematocrit group, and to the low-hematocrit group - attainment hematocrit level of 42% was related with 7% higher incidence of death in compare to low –hematocrit group. In high hematocrite group incidence of vascular-access thrombosis was significantly higher than in the low-hematocrit group. There was no statistically significant differences in non fatal myocardial infarction, stroke or
hospitalization rate between two groups [22]. The authors of the study concluded that detrimental outcomes were associated with a normal hematocrit level and the target hematocrit value of 42% cannot be recommended in patients with cardiac disease who are undergoing hemodialysis. The results of this study were in accordance with further outcomes of the CHOIR study and the CREATE study.

Safety Hb value during ESAs treatment in CKD patients on conservative treatment and these on renal replacement therapy is still matter of debate. According to NFK-DOQI guidelines from 2007 it was ascertain that Hb level should be greater than 11.0g/dl but less than 13.0g/dl because harm related with higher Hb level may be greater than benefits of such therapy in spite of quality of life improvement and avoidance of blood transfusion [13]. According to EBPG recommendations in individuals with diabetes or cardiovascular complications Hb level should be less than 12.0g/dl. Hb values above 14.0g/dl are not recommended. In each patient ESAs therapy should be individualized and concomitant diseases should be taken into consideration. In European guidelines, Hb value greater than 14.0g/dl is detrimental and such values may cause life threatening complications. As it was mentioned before the optimal Hb range is between 10g/dl to 12.0g/dl. Deleterious effects of ESAs treatment may be rather related with EPO overdosing/toxicity than high Hb level itself. [23].

CONCLUSIONS

1. High cardiovascular events rate in renal anemia patients may be rather related with oxidative stress and inflammation than anemia itself.
2. Complications of ESAs therapy and iron supplementation during renal anemia treatment may be related with ESAs/iron overload and toxicity.
3. Safety Hb range during ESAs treatment is estimated between 10g/dl to 12g/dl. Hb>12.0g/dl may be dangerous for CKD patients and higher cardiovascular events may be observed.

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