The challenges of anaemia management: from the guideline to the clinical practice

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Anaemia commonly accompanies chronic kidney disease (CKD) and is associated with reduced quality of life and increased mortality risk. Iron supplementation and erythropoiesis-stimulating agents (ESAs) have been the cornerstones of CKD-associated anaemia management for several decades. Recently, a new treatment option has emerged - Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors (HIF-PHIs), but their role in managing anaemia is still a matter of discussion.

What is the role of HIF stabilizers in the current anaemia treatment?

In order to gain a comprehensive perspective on this issue, it is imperative to reevaluate the fundamental objectives of anaemia treatment. Haemoglobin target levels have been thoroughly considered over the years, but the latest treatment goals have shifted towards considering patient-centric outcomes as well. Recent research shows that the CKD population prioritizes alleviating fatigue, improving life participation,

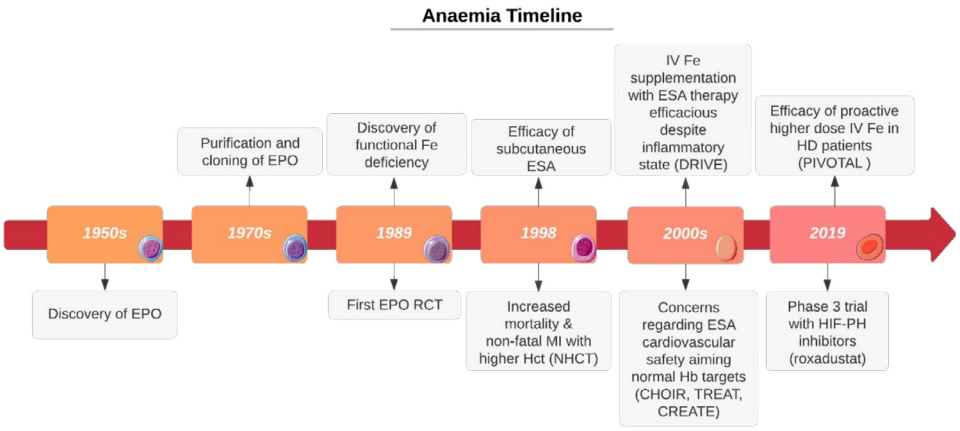

Figure 1.
CKD-associated anaemia treatment timeline

managing cardiovascular disease, reducing mortality, and ensuring functional vascular access for haemodialysis. Therefore, novel treatments are expected to fulfil these requirements as well, besides merely accomplishing certain haemoglobin values.

HIF stabilizers have been shown to correct anaemia, help maintain haemoglobin levels over time and decrease the share of patients requiring blood transfusions. They provide a more convenient mode of administration and may facilitate anaemia treatment in patients with non-dialysis-dependent CKD. Also, these agents potentially improve iron utilization for erythropoiesis, particularly oral iron. The trials consistently showed increased transferrin and total iron binding capacity and decreased ferritin and hepcidin with HIF-PHIs use, which is in keeping with better iron utilization.

Still, HIF stabilizers are not superior to ESAs in reaching the target haemoglobin concentrations, and they are not any safer. A Cochrane systematic review by Natale et al. found that compared to ESA, HIF-PHIs may have no effect on cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, while their impact on fatigue remains uncertain and requires further investigation. HIF-PHIs might have a role in ESA hyporesponsive or unresponsive patients, but the necessary doses in such cases consistently exceed those used in the efficacy trials thus presenting a possible safety issue.

Table 1 | Potential advantages and disadvantages of various CKD-anemia therapies

Agents	Potential advantages	Potential disadvantages
HIF-PHIs	• Oral dosing more convenient for some patients • May facilitate anemia treatment in patients with non–dialysis-dependent CKD • May improve utilization of iron for erythropoiesis, particularly oral iron • May be more effective in chronic inflammatory states (CRP >5 mg/l)	• Difficult to monitor adherence • Potential polypharmacy and drug–drug interactions • Less clinical experience • Potential risk of enhancing tumor growth • Potential risk of worsening retinopathy • Potential risk of cyst growth in ADPKD
ESAs	• Adherence can be monitored with in-clinic administration • Extensive clinical experience	• Treatment requires self-injection or regular clinic visits • Resistance in chronic inflammatory states • Risk of enhancing tumor growth • Antibody-mediated pure red cell aplasia (rare)
Iron compounds	• No serious adverse effects of oral iron	• If taken orally, risk of poor gastrointestinal tolerance and non-adherence to therapy • If i.v., risk of allergic/anaphylactic reaction • If i.v., potential risk of increasing oxidative stress • If i.v., potential risk of hemosiderosis

Figure 2.
Potential advantages and disadvantages of various CKD-associated anaemia therapies

Other potential limitations to HIF-PHI use include adherence issues, polypharmacy complexities, drug interactions, and limited clinical experience. Moreover, HIF-PHIs carry a latent risk of enhancing tumour growth by interfering with multiple signalling pathways and affecting cell differentiation and growth. Also, the upregulation of vascular endothelial growth factor by the HIF pathway may increase angiogenesis and therefore, in theory, worsen diabetic retinopathy and age-related macular degeneration. HIF activation occurs in polycystic kidneys in humans and rodents, and activation of the HIF pathway has been shown to enhance cyst expansion in preclinical models.

Regarding specific recommendations, HIF-PHIs may offer an alternative for people living with non-dialysis CKD. Oral administration eliminates the need for hospital visits thus adding more convenience. However, there is a possibility of an elevated risk of major adverse cardiovascular events (MACE), especially among non-dialysis CKD patients, and particularly those who recently experienced cardiovascular events. Therefore, this risk factor should be carefully considered at an individual level.

In the dialysis population, trials have demonstrated similar efficacy for HIF-PHIs in both hemodialysis and peritoneal dialysis patients. Notably, the non-inferiority margins for MACE were met in both dialysis modalities. Therefore, peritoneal dialysis and home hemodialysis patients could be treated with HIF stabilizers, if they felt strongly about an oral over the subcutaneous administration.

Besides HIF stabilizers several other agents are currently being investigated that might eventually contribute to more efficient anaemia management in the CKD population, such as hepcidin inhibitors, agents targeting proinflammatory cytokines IL1 and IL6, and new iron agents. Also, SGLT2 inhibitors appear to improve iron homeostasis and increase erythropoietin production in the kidneys thus resulting in higher hematocrit and haemoglobin levels.

Can we safely achieve normal haemoglobin in patients with CKD-associated anaemia?

Safely achieving physiological haemoglobin levels in CKD patients through pharmacological means is a complex issue in some CKD patients, particularly those with polycystic kidney disease (PKD). A quarter of a century ago Besarab et al. postulated that it is not advisable to raise hematocrit to normal levels among patients with clinically evident congestive heart failure or ischaemic heart disease on dialysis due to increased risk of death or myocardial infarction. Similarly, Singh et al. suggested that a higher haemoglobin target was associated with a higher rate of serious adverse events, death, myocardial infarction, and stroke, without a convincing improvement in quality of life or cardiovascular status. Although some experts attribute these effects to high ESA dosing rather than normal haemoglobin levels, the current guidelines suggest keeping haemoglobin and haematocrit at lower than physiological levels in the CKD population.

The complex relationship between haemoglobin levels and symptom relief, which can vary widely among individuals, calls into question the feasibility and desirability of establishing a universal haemoglobin threshold for CKD patients, despite anaemia's potential impact on symptoms and long-term well-being. Given the limited evidence that minor haemoglobin changes impact patient-important outcomes, such as cardiovascular health or eGFR loss, prioritizing the correction of anaemia to enhance individual patient well-being should be considered. This approach could involve achieving a haemoglobin level at which a patient's symptoms, such as fatigue, improve without continuously increasing ESA doses.

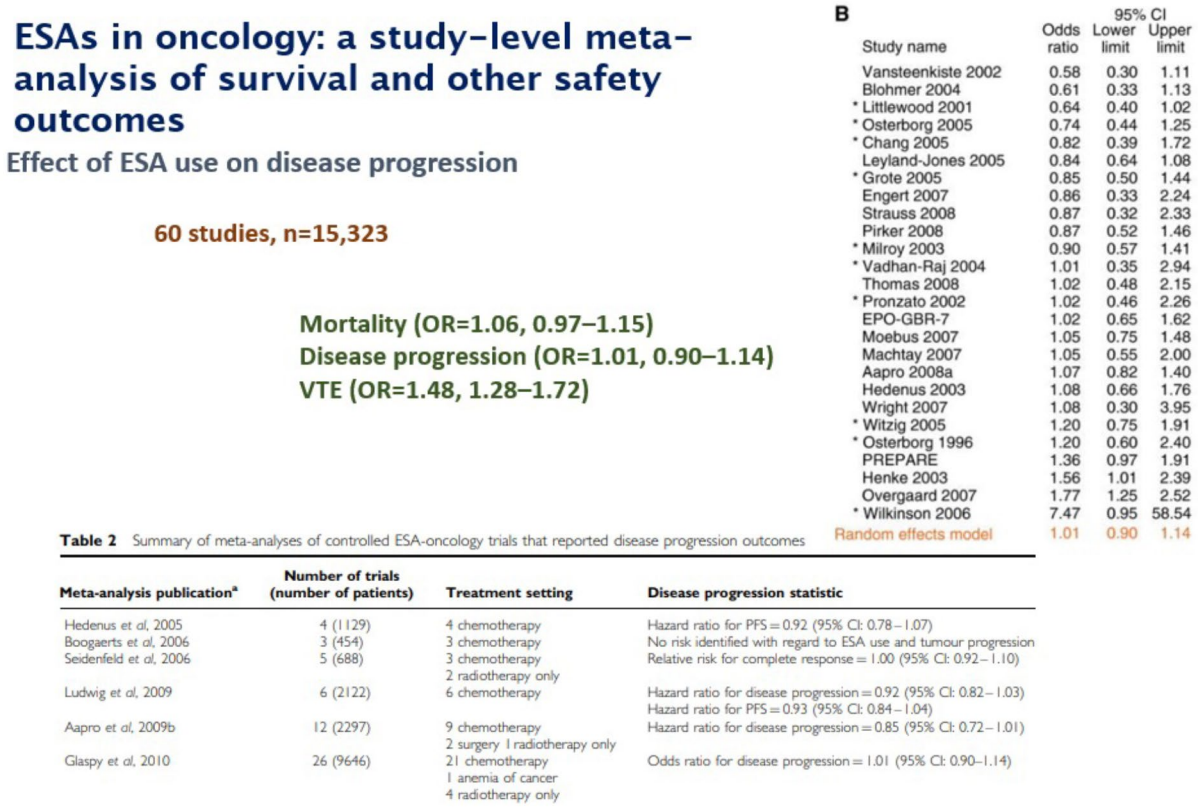

Table 2 Summary of meta-analyses of controlled ESA-oncology trials that reported disease progression outcomes

Meta-analysis publication[a]	Number of trials (number of patients)	Treatment setting	Disease progression statistic
Hedenus *et al*, 2005	4 (1129)	4 chemotherapy	Hazard ratio for PFS = 0.92 (95% CI: 0.78–1.07)
Boogaerts *et al*, 2006	3 (454)	3 chemotherapy	No risk identified with regard to ESA use and tumour progression
Seidenfeld *et al*, 2006	5 (688)	3 chemotherapy 2 radiotherapy only	Relative risk for complete response = 1.00 (95% CI: 0.92–1.10)
Ludwig *et al*, 2009	6 (2122)	6 chemotherapy	Hazard ratio for disease progression = 0.92 (95% CI: 0.82–1.03) Hazard ratio for PFS = 0.93 (95% CI: 0.84–1.04)
Aapro *et al*, 2009b	12 (2297)	9 chemotherapy 2 surgery I radiotherapy only	Hazard ratio for disease progression = 0.85 (95% CI: 0.72–1.01)
Glaspy *et al*, 2010	26 (9646)	21 chemotherapy 1 anemia of cancer 4 radiotherapy only	Odds ratio for disease progression = 1.01 (95% CI: 0.90–1.14)

Figure 3.
ESAs in oncology: effect of ESA use on disease progression

How do we approach CKD-associated anaemia in patients with malignancy?

The issue of anaemia in CKD patients with malignancies still presents a challenge and the data in this field are all the same limited. Defining CKD-related anaemia in this specific population and discriminating it from malignancy-associated anaemia resulting from chemotherapy represent complex issues. Establishing recommendations for this patient population hinges on the ability to differentiate these distinct situations, which presents a significant challenge.

A delicate equilibrium must be maintained when considering various risks in this context. That includes the assessment of potential consequences from lack of anaemia treatment, specifically, the implications of adhering to blood transfusions as opposed to adopting either ESAs or HIF inhibitors. Additionally, it is imperative to carefully evaluate the risk of tumour progression. Most notably, the risk of thromboembolism associated with the use of ESA must be carefully considered.

Aapro et al. summarised results from clinical and preclinical studies that evaluated whether ESAs affect cancer progression. Current meta-analyses reveal no overall impact of erythropoiesis-stimulating agents (ESAs) on disease progression, although some individual studies suggest potential effects in specific cancer patient subsets. Despite theoretical concerns about ESAs indirectly influencing tumours through increased red blood cell production, current preclinical evidence contradicts this notion, as it suggests that tumour cells either lack erythropoietin receptors (EpoR) or have non-functional EpoR molecules. Therefore, ESAs do not appear to activate EpoR on tumour cells or stimulate disease progression through angiogenesis.

Clinical guidelines often rely on randomized controlled trial data. However, these trials fall short in addressing certain critical questions as they often insufficiently consider health-related quality of life and fatigue and fail to pinpoint the haemoglobin level at which incremental increases cease to translate into symptom improvement. Both randomized trials and observational data are needed to tackle these points, particularly in dialysis populations. Sequential randomized trials and sophisticated causal methodology can help identify individualized deflection points based on diverse patient characteristics, aligning with the principles of personalized medicine.

Written by: Jasna Trbojevic-Stankovic.
All the speakers reviewed and approved the content

KEY POINTS

1. Empirical evidence does not strongly support HIF-PHIs over ESAs in terms of quality of life or safety.

2. Achieving normal haemoglobin levels in CKD patients is complex. Studies found no clear advantage from targeting higher haemoglobin levels, thus emphasizing a cautious approach.

3. Careful consideration of the risks and benefits of anaemia treatment in patients with malignancies is essential, along with assessing the associated risk of tumour progression and thromboembolism.

4. Clinical guidelines often lack comprehensive data on health-related quality of life, fatigue, and optimal haemoglobin levels. Addressing this challenge requires a combination of results from randomized trials and observational data, particularly in dialysis populations.

Further readings

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