Past, present and future of erythropoietin use in anemia in older adults

The Ageing Process: Does it Matter when Considering Lymphoproliferative Disorders and Supportive Care?

Lisboa, October 23rd from 15.30 – 17.00

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# Disclosures – Reinhard Stauder

<table>
<thead>
<tr>
<th>Category</th>
<th>Companies</th>
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<tr>
<td>Research Support/P.I.</td>
<td>Celgene, Novartis, Teva</td>
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<td>Employee</td>
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Anemia in the elderly

Intro
Definition
Prevalence & relevance
Causes and classification
Therapy with focus on erythropoietins
  - Anemia of chronic disease (ACD)
  - Anemia of chronic kidney disease (CKD)
  - Cancer-related or chemotherapy-induced anemia (CRA, CIA)
  - Myelodysplastic Syndromes (MDS)
Conclusions
# Recombinant erythropoietins in the EU

<table>
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<th>Generic name</th>
<th>Trade name</th>
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<tr>
<td></td>
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<td>CKD</td>
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<td>1st generation</td>
<td>Epoetin alfa</td>
<td>Epoetin alfa Hexal&lt;sup&gt;*&lt;/sup&gt;</td>
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<td>Binocrit&lt;sup&gt;*&lt;/sup&gt;</td>
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<td>Epoetin beta</td>
<td>NeoRecormon&lt;sup&gt;*&lt;/sup&gt;</td>
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<td>Methoxy polyethylene glycol-epoietin beta</td>
<td>Mircera&lt;sup&gt;*&lt;/sup&gt;</td>
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</table>

CKD, chronic kidney disease; Cancer-related or chemotherapy-induced anemia (CRA, CIA); Anemia of chronic disease (ACD); Myelodysplastic Syndromes (MDS)

* A starting dose of 20,000 IU/w is sufficient in a relevant proportion of patients (Tjulandin SA, et al. Arch Drug Inf. 2011;4(3):33-41.)
Anemia in the elderly

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- Causes and classification
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Anemia in the elderly – definition

- **WHO definition**¹
  - Hb <13 g/dL (<130 g/L) men
  - Hb <12 g/dL (<120 g/L) non-pregnant women
  - Challenge: established in 1960s in persons <65 yrs
  - Widespread definition

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Anemia in the elderly – prevalence

- WHO criteria (♀< 12 g/dL; ♂< 13 g/dL)
- Data poled from 45 studies (n = 85,400)

<table>
<thead>
<tr>
<th>POPULATION</th>
<th>ANEMIA PREVALANCE (%)</th>
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<td>Elderly living in community</td>
<td>12</td>
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<tr>
<td>Hospital admission</td>
<td>40</td>
</tr>
<tr>
<td>Elderly in nursing home</td>
<td>47</td>
</tr>
<tr>
<td>All studies</td>
<td>17</td>
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</tbody>
</table>

Anemia in the elderly – prevalence

- Late-life anemia is frequent
- About 15 million citizens 65+ years in European Union are affected (based on prevalence of 17% in elderly\(^1\))
- Anemia increases dramatically with advanced age reaching a prevalence of nearly 50% in elderly men
- Number will increase in the next years due to ageing of societies

Anemia impacts hospitalization & mortality

- Anemia is correlated with increased hospitalization (HR 2.7; 95% CI: 2.5-2.9) and mortality (HR 5.0; 95% CI: 4.4-5.7).
- Optimal Hb-value in elderly is 13-15 w and 14-17g/dL m
- New definition based on favourable outcome?

- 17,030 community-dwelling persons; 66+ yrs
- Based on Calgary lab. data services, Canada

Anemia in the elderly – clinical relevance

Anemia has been associated with

- increased morbidity, mortality, and hospital stays
- higher incidence of cardiovascular disease, cognitive impairment, decreased physical function, and quality of life
- increased risk of falls and fractures
- might be an early sign of an undiagnosed malignant disease

Despite clinical importance, anemia is often neglected and evidence-based guidelines are lacking

Anemia in the elderly

Intro

Definition

Prevalence & relevance

Classification and therapy with focus on erythropoietins

- Anemia of chronic disease (ACD)
- Anemia of chronic kidney disease (CKD)
- Unexplained anemia (UA)
- Myelodysplastic Syndromes (MDS)
- Cancer-related or chemotherapy-induced anemia (CRA, CIA)

Conclusions
Anemia in the elderly – possible causes

- Nutrient deficiency
  - Iron (iron deficiency anemia = IDA)
  - Vitamin $B_{12}$, Folate
- Anemia of chronic disease (ACD), anemia of (chronic) inflammation (A(C)I), & anemia secondary to chronic kidney disease (CKD)
- Unexplained anemia (UA) prevalence 34-44%
- Cancer-related/chemotherapy-induced anemia (CRA, CIA)
- Myelodysplastic Syndromes (MDS)

Iron deficiency anemia (IDA)

- **Absolute IDA**
  - Serum ferritin low
    - <30 mcg/L if no inflammation
    - <100 mcg/L in inflammatory status (ferritin-levels rise with inflammation & age)
  - Low transferrin saturation (<20%)
  - Determine site of blood loss!
  - Treat by iron supplementation

- **Functional IDA**
  - Low transferrin saturation (<20%)
  - Serum ferritin >30 mcg/L (>100 mcg/L in inflammation)

Anemia of chronic disease (ACD)

- Includes anemia secondary to inflammation, auto-immune disease, malignancy, chronic kidney disease (CKD), advanced age, heart failure...

- Mediators of hyperinflammation
  - Interleukins (eg, IL-1 and IL-6) & tumor necrosis factor (TNF-alpha)
  - Hepcidin, CRP....

- Relative decrease in EPO production & blunted response to EPO

- Functional (relative) iron deficiency (trapping of iron in RES)

Therapy

- Treat underlying cause
- ESAs ± iron?
- Anti-hepcidin approaches

RES, reticuloendothelial system
Hepcidin – regulator of iron hemostasis

RBCs, red blood cells; Fe-Tf, iron-transferrin complex.

Anemia secondary to chronic renal disease (CKD)

- Reduction in functioning renal mass results in reduced glomerular filtration rate and low EPO-levels (threshold?)
- Anemia is common in CKD even in predialysis patients
- Prevalence increases as GFR declines <60 mL/min/1.73 m²

Association of kidney function with anemia
Decrease of Hb even in mild renal insufficiency

Predicted prevalence of hemoglobin level <11, <12, and <13 g/dL in persons ≥ 20 years.
Estimates and 95% confidence intervals are demarcated.

Anemia secondary to chronic renal disease (CKD)

- ESAs are active\(^1,2\) and registered in this type of anemia (threshold? “renal failure”, “renal insufficiency”)
- Non-renal causes of anemia should be excluded (iron status, B12, folate, bleeding)
- CKD patients often suffer from iron deficiency
- Recommendations from relevant societies exist\(^3\)
  - Indication for treatment: symptoms attributable to anemia, Hb<10g/dL\(^4\)
  - Hb target: maintain 10.0-11.5 g/dL; not >13g/dL\(^4\)
  - Hb targets should be achieved with lowest effective ESA doses as cumulative high ESA doses seem to be associated with an increased risk of mortality, cardio- and cerebrovascular events as determined in pooled analyses\(^4\)
  - Escalation of ESA doses in patients with poor ESA response should be avoided\(^4\)

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\(^{4}\) 10 July 2014. EMA/PRAC/418466/2014. Patient Health Protection
ESAs in anemia in elderly

- Data are rare and definition of anemia of included patients is often vague
- Double-blind, placebo-controlled, crossover exploratory study with epoetin alfa
  - 62 community-dwelling persons 65+ yrs with chronic anemia (Hb ≤11.5 g/dL); predominantly African-American women
  - 69% of EPO-patients responded
  - Direct relationship between increases in Hb during ESA-therapy and improvements in fatigue and QOL
- Excluded were:
  - history of bleeding or bleeding disorders; active cancer; GFR less than 30 mL/min per 1.73m²; iron, vitamin B12, or folate deficiency; uncontrolled hypertension; hospitalization within 1 month
  - bone marrow biopsy was not conducted to exclude MM or MDS; any patient who had abnormal serum proteins, thrombocytopenia, or neutropenia was also excluded

ESAs in anemia in elderly

- Correction of Anemia in the Frail Elderly (CAFÉ): Results of a Randomized, Double-Blind, Placebo-Controlled Study with Darbepoetin Alfa in Elderly Patients with Chronic Unexplained Anemia\(^1\)
  - Double-blind, placebo-controlled clinical trial
  - 80 community-dwelling, pre-frail or frail (Hopkins Frailty Index score 1 to 3) patients 70+ yrs with chronic anemia (Hb <11.5 g/dL)
  - Significantly greater hematopoietic response (mean 1.13 ± 0.59 g/dL) in the participants treated with DA than in those receiving placebo (0.3 ± 0.18 g/dL)

ESAs in anemia in elderly

- Congestive heart failure (CHF)$^1$
  - Double-blind randomised study on darbepoietin alfa in systolic heart failure (EF<40%); Hb 9-12 g/dL
  - Early and sustained increase in Hb values; symptoms improved
  - Clinical outcome (death or hospitalization) not altered
  - Thromboembolic events increased (13.5 vs 10%; p=0.01)

Treatment of anemic low-risk MDS (IPSS Low-grade and Int-1)

Symptomatic anemia

Supportive therapy including transfusions & iron-chelation

- Del(5q)
  - Lenalidomide
  - ESA

- EPO < 500 U/L and/or low transfusion need (<2U/month)
  - ESA ± G-CSF

- EPO ≥ 500 U/L and/or high transfusion need
  - Valproic acid
  - (Azacitidine)
  - (Lenalidomide)

Recommendations of the Austrian MDS-Platform

- Hypoplastic MDS HLA-DR15
  - CyA (ATG)

ESAs in MDS

- Reduce transfusion need and increase Hb-levels and QoL in low-risk MDS
- No evidence for negative impact on survival or AML evolution in prospective\(^1\) or historical controls\(^2,3\)
- ESAs even improve survival in treated patients\(^2,3\); however, improvement in prospectively randomized trials has so far not been shown\(^1\)
- A predictive model exists (Nordic score)\(^4\)
- Low IPSS-R, low serum EPO, and low serum ferritin are significantly associated with better erythroid response\(^5\)
- Results of two prospective phase III trials will be presented at ASH 2014

Cancer-related/chemotherapy-induced anemia (CRA, CIA)

- Frequent complication (European Cancer Anemia Survey [ECAS])\(^1\)

  ![Hemoglobin Levels](image)

  - Hb ≥ 12 g/dl: 61%
  - Hb 10.0-11.9 g/dl: 29%
  - Hb 8.0-9.9 g/dl: 9%
  - Hb <8.0 g/dl: 1%

- Associated with fatigue, impaired physical function and reduced QoL

### Guidelines on ESAs in CIA

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>ASCO/ASH(^1)</th>
<th>NCCN(^2)</th>
<th>EORTC(^3)</th>
<th>ESMO(^4)</th>
<th>EORTC(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When to start</strong></td>
<td>Hb ≤ 10 g/dL (clinical decision if Hb 10-12 g/dL)</td>
<td>Hb ≤ 11 g/dL</td>
<td>Hb 9-11 g/dL (clinical decision if Hb ≤ 11.9 g/dL)</td>
<td>Hb ≤ 10 g/dL</td>
<td>Hb ≤ 10 g/dL</td>
</tr>
<tr>
<td><strong>Target range</strong></td>
<td>Lowest Hb level needed to avoid transfusions</td>
<td>Maintain 10-12 g/dL</td>
<td>Symptomatic patients target Hb should be around 12 g/dL</td>
<td>Should not exceed 12 g/dL</td>
<td>10-12 g/dL</td>
</tr>
<tr>
<td><strong>General recommendation</strong></td>
<td>• Iron deficiency should be corrected before ESA treatment</td>
<td></td>
<td>• Benefits of ESA-therapy should be carefully weighed along with its safety concerns when determining anaemia treatment options</td>
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### Potential new parameters in the classification of AE

<table>
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<th>Parameter</th>
<th>Comments</th>
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</table>
| Serumb feritin<sup>1</sup> | Low levels indicate IDA  
Normal levels do not rule out an IDA, as ferritin represents an acute phase reactant |
| Transferrin saturation (TSAT)<sup>2</sup> | Reduced in ID and in ACD |
| Reticulocyte hemoglobin content (CHr)<sup>3</sup> | Short term indicator of ID erythropoiesis |
| Inflammation markers (CRP, IL-6, ....)<sup>4</sup> | Useful in the definition of ACD |
| Erythropoietin (EPO)<sup>5</sup> | Glycoprotein growth factor that is the primary stimulus of erythropoiesis |
| Hepcidin<sup>6</sup> | Acute phase peptide produced in liver; key negative regulator of intestinal iron adsorption and iron release from RES and enterocytes; mutations cause juvenile hemochromatosis  
Different techniques of measuring serum hepcidin levels (ELISA, mass spectrometry) not generally available and not standardized yet |
| Ferroportin<sup>7</sup> | Cellular iron exporter, is regulated by hepcidin |
| Erythroferrone (Erfe)<sup>8</sup> | Erythroid regulator; suppresses hepcidin |
| Hemojuvelin<sup>9</sup> | Cell-bound form: relevant positive regulator of hepcidin, coreceptor of BMP6  
Soluble form (sHJV): produced by cleavage in hypoxia and in iron deficiency, downregulates hepcidin, ELISAs available |
| Bone morphogenetic protein 6 (BMP6)<sup>10</sup> | Cytokine produced in iron overload, coreceptor of hemojuvelin, induces hepcidin activation |
| Hepcidin/ferritin ratio<sup>11</sup> | A measure of adequacy of hepcidin levels relative to body iron stores |
| Hephaestin<sup>12</sup> | Transmembrane ferroxidase in enterocytes, transporting dietary iron into the circulation |

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<sup>1</sup>Ikram & Hassan. Haematology Updates. 2011;17-22;  
<sup>2</sup>http://www.irondisorders.org/anemia-of-chronic-disease;  
<sup>4</sup>Greer J, et al. Wintrobe’s Clinical Hematology;  
<sup>5</sup>Erslev A. N Engl J Med. 1991;324:1339-44;  
<sup>6</sup>http://www.ifcc.org/ifccfiles/docs/publications/eJIFCC/vol20/02/eJIFCC-02-02.pdf;  
<sup>8</sup>Kautz L, et al. Nat Genet. doi: 10.1038/ng.2996. [Epub ahead of print];  
<sup>9</sup>Zhang A. Adv Nutr. 2010;1:38-45;  
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Conclusions
Anemia in the elderly (AE) – Conclusions 1

- Relevant challenge for individual, society and hematologists
- Underlying mechanisms are complex & so far poorly defined
- ESAs are, and will be, relevant in the treatment of AE

<table>
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<tr>
<th>Type of anemia</th>
<th>Evidence 1-4</th>
<th>Guidelines</th>
<th>Registration</th>
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<tr>
<td>Chronic kidney disease</td>
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<td>+++</td>
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</tr>
<tr>
<td>Anemia of chronic disease</td>
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<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Unexplained anemia</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
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<tr>
<td>Chemotherapy-induced anemia</td>
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Anemia in the elderly (AE) – Conclusions 2

- Goal is the definition of refined pathologic algorithms based on new parameters; these will form the basis for evidence-based clinical strategies and clinical studies including ESA

- Outcome measures relevant for elderly should be integrated including functional capacities and patient-reported outcomes (PROs) like QoL

- Possible side effects of ESAs, particularly hypertension, thrombo-embolic complications, flu-like illness & headache have to be considered and discussed with patient
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