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

Welcome and introduction
Matti Aapro

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Agenda
- Adapting lymphoproliferative treatment in older adults
  - Ruth Pettengell, UK
- Chemotherapy-induced neutropenia and the role of G-CSF in older patients
  - Antonio Pinto, Italy
- Past, present and future of erythropoietin use in anaemia in older adults
  - Reinhard Stauder, Austria
- Panel Q&A session
  - All faculty
- Closing remarks
  - Matti Aapro, Switzerland

Web key & evaluation form
Please complete and return your evaluation form after the symposium to receive your complimentary Web key, containing the abstract and key slides from each presentation.
Adapting lymphoproliferative treatment in older adults

Dr Ruth Pettengell

Disclosures

• Speaker’s honorarium: Teva

Determining Treatment Goals in Older Patients

Frailty is Associated with . . .

Remaining Life Expectancy
Cardiovascular Health Study
(n = 5317, >65 y)

Frailty Pathophysiology

COMPREHENSIVE GERIATRIC ASSESSMENT = gold standard
Age-related Changes in Elderly

Potential Effect of Statins on Rituximab

Rituximab Clearance in DLBCL According to Age and Gender

Vit D Insufficiency and Survival Outcome in CLL

Randomized Phase III Trials in CLL

First-Line FCR vs BR in Fit Patients CLL
Fludarabine vs Chlorambucil in Elderly CLL: OS

![Graph showing OS comparison between Fludarabine and Chlorambucil.]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OS (months)</th>
<th>P value</th>
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<td>Chlorambucil</td>
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<td>Fludarabine</td>
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Obinutuzumab plus Chlorambucil in Frail CLL pts

<table>
<thead>
<tr>
<th>Group</th>
<th>OS (months)</th>
<th>PFS (months)</th>
<th>Rates of death</th>
<th>Neutropenia (%)</th>
<th>Anemia (%)</th>
<th>Thrombocytopenia (%)</th>
<th>Infections (%)</th>
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<tr>
<td>Chlorambucil+Ch</td>
<td>N = 116</td>
<td>N = 336</td>
<td>N = 321</td>
<td>16</td>
<td>4</td>
<td>4</td>
<td>14</td>
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<tr>
<td>Obinutuzumab+Ch</td>
<td>N = 336</td>
<td>N = 336</td>
<td>N = 321</td>
<td>33</td>
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<td>4</td>
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<td>Rituximab+Ch</td>
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<td>N = 321</td>
<td>28</td>
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Lenalidomide as Initial Therapy in Elderly CLL

<table>
<thead>
<tr>
<th>Group</th>
<th>OS @ 4 yr</th>
<th>PFS @ 4 yr</th>
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<th>Hematologic toxicity</th>
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<td>Rituximab+Ch</td>
<td>88%</td>
<td>57%</td>
<td>65-71 y 72%, 72+ y 57%</td>
<td>Grade 2-3</td>
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<tr>
<td>GA101+Ch</td>
<td>88%</td>
<td>57%</td>
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Lenalidomide-Rituximab in R/R CLL

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<tr>
<th>Group</th>
<th>OS NR</th>
<th>OS 71% @ 36 mo</th>
<th>PFS 17.4 mo</th>
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<tr>
<td>Rituximab+Ch</td>
<td>71%</td>
<td>75%</td>
<td>96%</td>
<td>96%</td>
<td>75%</td>
</tr>
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<td>75%</td>
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</tr>
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Ibrutinib Monotherapy in CLL

<table>
<thead>
<tr>
<th>Group</th>
<th>OS @ 26 mo</th>
<th>ORR @ 26 mo</th>
<th>PFS @ 26 mo</th>
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<tr>
<td>Treatment naive</td>
<td>96%</td>
<td>75%</td>
<td>≥86%</td>
</tr>
<tr>
<td>R/R or HR</td>
<td>96%</td>
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</table>

Ibrutinib Monotherapy in CLL: AEs ≥ Grade 3

Ibrutinib vs Ofatumumab in R/R CLL: Interim Analysis

Ibrutinib Monotherapy vs Ofatumumab in R/R CLL:

Ibrutinib Monotherapy in CLL: AEs ≥ Grade 3

Ibrutinib Monotherapy vs Ofatumumab in R/R CLL: Interim Analysis

Rituximab + Idelalisib in Frail Elderly

<table>
<thead>
<tr>
<th>AE</th>
<th>Ibrutinib</th>
<th>Ofatumumab</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>47.7</td>
<td>17.6</td>
<td>0.001</td>
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<tr>
<td>Fatigue</td>
<td>27</td>
<td>29.8</td>
<td>0.70</td>
</tr>
<tr>
<td>Nausea</td>
<td>26.2%</td>
<td>18.3%</td>
<td>0.02</td>
</tr>
<tr>
<td>P. neuropathy</td>
<td>37%</td>
<td>42%</td>
<td>0.04</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>104%</td>
<td>100%</td>
<td>1</td>
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<tr>
<td>Neutropenia</td>
<td>16%</td>
<td>14%</td>
<td>0.12</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7%</td>
<td>5%</td>
<td>0.12</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6%</td>
<td>4%</td>
<td>0.12</td>
</tr>
</tbody>
</table>

| Rituximab + Idelalisib (n = 110) |
|-------------------------------|----------------|
| R = Placebo (n = 110) | R = Idelalisib (n = 110) |
| ORR                          | 13% | 75% |
| PFS at 24 wk                 | 50% | 90% |
| Median PFS                   | 5.5 mo | NR |
| OS @ 24 wk                   | 86% | 96% |

- Median age 71 y (78% over 65 y)
- AEs ≥ grade 3
  - Thrombocytopenia 11%, anemia 7%
  - Diarrhea (4%), pyrexia (3%), chills (2%), fatigue (5%), rash (1%), pneumonia (8%)
- Improvement HRQOL and symptom control at 8 weeks
CAL-101 has Been Well Tolerated in Patients with CLL over Exposure Periods >1 year

- Grade 3-4 adverse events largely due to prior therapy or underlying CLL
- No maximum tolerated dose or dose-limiting toxicities
- No pattern of drug-related symptomatic adverse events

Grade 3-4 adverse events occurring in ≥5% of patients regardless of causality (N = 55)

Progression-Free Survival of Total Group*

*ITT analysis of primary + extension study. Extension data based on unscheduled investigator assessments.

Conclusions

- Frailty is a better indicator of fitness and life expectancy
- Few treatment options for the frail elderly
- Integrated mutational and cytogenetic analysis to identify prognostic subgroups in elderly CLL
- BCR p/w inhibitors: oral, excellent bulk reduction including high-risk pts; to date, favorable SE profile
- Toxicity of chemotherapy vs targeted therapy??
- We need clinical trials in the elderly!!!!!
Disclosures

- Speaker’s honorarium – Teva, Roche, Celgene, Mundipharma

Fighting Ageism in Medicine: The Case of Aggressive NHL

A woman tells her doctor: “Doc, I have got a very bad pain in my left knee.”

The doctor replies: “It’s normal, mum … you’re 80 years old.”

…and the woman replies: “That’s true doc … point is that my right knee is also 80 years old … but it doesn’t hurt.”

G-CSF Use in Haematopoietic Tumours: The Case of Aggressive NHL & Hodgkin Lymphoma

- Aggressive NHL (DLBCL) & HL
  - A paradigm for “curable” cancers
  - A paradigm for “cancer in the elderly”
  - A paradigm for “optimal use” of G-CSF

- G-CSF and aggressive NHLs & HL in the elderly
  - G-CSF may be integral to some chemotherapy programs
  - G-CSF may be mandatory to achieve the target of “cure”
  - Young and elderly patients
  - G-CSF may be a requisite to reduce “early” treatment-related morbidity and mortality
  - G-CSF is a pre-requisite to “get rid” of the “First Cycle Effect”

Challenges in Aggressive Lymphomas

All aggressive lymphomas are equal but some aggressive lymphomas are more equal than others

R-CHOP studies >60 yrs: How many patients will relapse?

<table>
<thead>
<tr>
<th>Low-risk patients</th>
<th>High-risk patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse rate</td>
<td></td>
</tr>
<tr>
<td>40% - 60%</td>
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</tbody>
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Challenges in Aggressive Lymphomas

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**R-CHOP & MYC Rearranged DLBCL**

- 35 (14%) with MYC rearrangements
  - 74% of cases with MYC rearrangement had concurrent t(14;18)
  - 26% of cases with MYC rearrangement had a BCL6 translocation

**R-CHOP & MYC: Interaction with IPI and Age**

- FISH Model
- IHC Model

**Challenges in Aggressive Lymphomas**

- All patients with aggressive lymphomas are equal but some patients with aggressive lymphomas are more equal than others

**Patient-Related Factors Associated with an Increased Risk of FN**

- Risk factors for neutropenic events
  - Age >65 years
  - Female sex
  - Poor performance and/or nutritional status
  - Advanced disease
  - Prior infection
  - Previous FN episode(s)
  - Prior chemotherapy
  - No prior G-CSF use
  - No antibiotic prophylaxis
  - Body surface area <2.0 m²
  - One or more comorbid disease, particularly
    - Cardiovascular disease
    - Renal disease
    - Liver disease (abnormal liver transaminases)
    - Haemoglobin <12 g/dL

- Older age, poor performance status, and active disease are associated with an increased risk of neutropenia

**Patient Age at Diagnosis Is Associated with the Molecular Characteristics of DLBCL**

Some molecular features correlating with age:

- ABC subtype
- Bcl-2 expression
- Cytogenetic complexity
- IRF4 translocations
- Gains 1q21, 18q21, 7p22, and 7q21
- Changes in 3q27/affecting the BCL6 locus

**BUT NO cut-off (spectrum...)**

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**R-CHOP & MYC: Interaction with IPI and Age**

![Graph showing R-CHOP & MYC interaction with IPI and Age]

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**Impact of MYC Status in DLBCL**

**Prognostic Indices**

<table>
<thead>
<tr>
<th>aIPI</th>
<th>90% 3 yr survival</th>
<th>70% 3 yr survival</th>
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<tbody>
<tr>
<td>aIPI = 2</td>
<td>90% 3 yr survival</td>
<td>70% 3 yr survival</td>
</tr>
<tr>
<td>Low-int risk (61-80)</td>
<td>71% 5 yr survival</td>
<td>52% 5 yr survival</td>
</tr>
<tr>
<td>High risk (61-80)</td>
<td>56% 3 yr survival</td>
<td>32% 5 yr survival</td>
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<td>ABC type</td>
<td>56% 3 yr survival</td>
<td>32% 5 yr survival</td>
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<tr>
<td>MYC breakpoint</td>
<td>56% 3 yr survival</td>
<td>32% 5 yr survival</td>
</tr>
<tr>
<td>Double hit</td>
<td>&lt;1.5 yr medial survival</td>
<td>&lt;1.5 yr medial survival</td>
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**Treatment Strategy in DLBCL**

- **Induction:** R-chemo
- **Consolidation:** RT/SCT
- **Maintenance:**
  - Tumour load reduction
  - Dose-intensity
  - Convert PR → CR
  - Eliminate MRD
  - Maintain optimal RDI (≥90%)

---

**DLBCL: Maintaining Dose Intensity Remains of Critical Importance in the Rituximab “Era”**

- RDI should ideally approach 100% (≥90%) regardless of the regimen
- Overstepping RDI of a given regimen is a concept (ie, R-CHOP14/21)
- Maintaining optimal RDI (≥90%) of each given regimen is a different story
  - R-CHOP21 (≥90%)
  - R-CHOP14 (≥90%)

---

A model based on data from 2500 patients with cancer receiving chemotherapy demonstrates that FN risk is greatest in the first chemotherapy cycle.


- Neutropenia is a frequent complication of chemotherapy associated with life-threatening infections, hospitalization, chemotherapy dose reduction and/or delay
- G-CSF administration reduces the duration and the degree of neutropenia in cancer patients who receive chemotherapy with a curative intent
- Current guidelines recommend the use of G-CSF in cancer patients with substantial risk of febrile neutropenia
- G-CSF integration into CT regimens for chemo-sensitive cancers (ie, amenable to be cured) may be necessary to
  I. Overstep the RDI of a given regimen
  II. Maintain the optimal RDI of the same regimen

G-CSF Use in Haematopoietic Tumours: The Case of Aggressive Lymphomas

- CR rate: 70%-83%
- 3-5 yr PFS/EFS: 53%-62%
- 5-10 yr OS: 58%-72%
- CR rate: <50%
- 3-5 yr PFS/EFS: <50%
- 5-10 yr OS: 58%-60%

CR rate: 78%
3-5 yr PFS/EFS: 66%-73%
5-10 yr OS: 68%-72%

R-CHOP21
R-CHOP14
R-CHOP22-25-28...

Impact of MYC Status in DLBCL: age & PS lose prognostic impact if adequate treatment is delivered

- DHL represents an unmet medical need

Rationale for using G-CSF

G-CSF Use in Haematopoietic Tumours: The Case of Hodgkin Lymphoma in Older Patients

Overall survival of older patients with Hodgkin lymphoma (HL) compared with an age- and sex-matched (ASM) population

Cumulative incidence of progression of older patients with Hodgkin lymphoma as determined by competing risk analysis


ABVD: Dose delivery and protocol adherence according to stage and age. Lines indicate mean relative doses. HD10 (favorable early-stage) ; HD11 (unfavorable early-stage patients) German Hodgkin Study Group


Use of G-CSF impacts

– Guidelines recommend primary prophylaxis with G-CSF to support R-CHOP delivery in pts with a ≥20% risk of febrile neutropenia
– These guidelines are not followed in clinical practice in a sizeable proportion of younger and older patients with DLBCL and HL
– Older patients are at high risk for neutropenia and FN-related morbidity
– Lack of adequate G-CSF support during R-CHOP /ABVD has negative implications for chemotherapy delivery. Maintaining a RDI of 290% has been shown to improve overall survival in NHL & HL
– Better adherence to guidelines for the use of prophylactic G-CSF during chemotherapy could improve the outcome and care of patients with DLBCL & HL


• Use of G-CSF impacts

Aggressive NHL (DLBCL and variants; BL) are curable diseases

– Presence of some biologic risk factors (ABC vs GC, C-MYC overexpression, DH, etc) display an age-associated incidence
– While R-CHOP is unsatisfactory in high-risk patients, unsatisfactory-delivered (R-CHOP21/14) will surely prevent a number of patients from being cured (especially the elderly)
– While R-CHOP21 and R-CHOP14 are equivalent, dose-intensity remains a prerequisite for cure
– Since most toxic and therapy-delaying events occur during the first chemotherapy cycles, primary G-CSF prophylaxis is mandated in high-risk patients (young and old) and in all aged patients
– Few “well-administered” (dose-intense) courses are maybe more useful than 6 or 8 “badly-administered” (with accumulating delays) cycles


Just to Sum Up

G-CSF Use in Haematopoietic Tumours: The Case of Hodgkin Lymphoma in Older Patients

G-CSF Impacts

• Use of G-CSF impacts

– Guidelines recommend primary prophylaxis with G-CSF to support R-CHOP delivery in pts with a ≥20% risk of febrile neutropenia
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• Human endogenous G-CSF

– G-CSFs are naturally (glyco)sylated in mammalian cells post-translation

• Recombinant G-CSFs

– E.Coli does not have the mechanisms to glycosylate G-CSF
– Recombinant G-CSFs produced in E. coli are not glycosylated

• Short-acting G-CSFs

– Filgrastim (unglycosylated; E.Coli-derived)
– Pegfilgrastim (PEGylated)
– GlycoPEGylated
– LipePEGylated

• Long-acting G-CSFs

– Pegfilgrastim
– FigePEGylated
– GlycoPEGylated
– LipePEGylated


G-CSF & G-CSFs: Short- and Long-Acting Variants
The artist Michele Angelo Petrone, who died at age 43 following admission to hospital with a chest infection, transformed the lives of countless cancer patients and their carers by showing how painting could be used to express their fears about illness and death.

He had suffered from Hodgkin’s disease for many years, and established a foundation that will carry his work forward.

Past, Present, and Future of Erythropoietin Use in Anemia in Older Adults

The Aging Process: Does It Matter when Considering Lymphoproliferative Disorders and Supportive Care?

Lisboa, October 23, from 15.30 – 17.00

Reinhard STAUDER MD, MSc, Associate Professor
Department of Internal Medicine V (Hematology and Oncology)
Innsbruck Medical University
Anichstraße 35, 6020 Innsbruck, Austria
reinhard.stauder@i-med.ac.at

Anemia in the elderly

Intro
Definition
Prevalence and 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>Type</th>
<th>Generic name</th>
<th>Trade name</th>
<th>Registered in</th>
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<td></td>
<td></td>
<td></td>
<td>CKD</td>
</tr>
<tr>
<td>1st generation</td>
<td>Epoetin alfa</td>
<td>Epoetin alfa Hexal® Abseamed® Assur®</td>
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<tr>
<td></td>
<td>Epoetin beta</td>
<td>NeoRecormon®</td>
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<td></td>
<td>Epoetin alfa</td>
<td>Retacrit® Haemag®</td>
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<tr>
<td></td>
<td>Epoetin beta</td>
<td>NeoRecormon®</td>
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<tr>
<td></td>
<td>Epoetin theta</td>
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<td>2nd generation</td>
<td>Darbepoetin alfa</td>
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<td></td>
<td>Methoxy polyethylene glycol-epoetin beta</td>
<td>Mircera®</td>
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Research Support/PI
- Celgene, Novartis, Teva

Employee
- 0

Consultant
- 0

Major Stockholder
- 0

Honoraria
- Celgene, Novartis, Teva

Scientific Advisory Board
- Celgene

Disclosures – Reinhard Stauder

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Conclusions
Anemia in the elderly – definition

- WHO definition¹
  - 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 yr
  - Widespread definition


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 elderly¹)
- Anemia increases dramatically with advanced age, reaching a prevalence of nearly 50% in elderly men
- Number will increase in the next years due to aging of societies


Anemia impacts hospitalization and 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 14-17 g/dL m.
- New definition based on favorable outcome?

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 and 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

Nutrient deficiency
- Iron (iron deficiency anemia = IDA)
- Vitamin B12, folate
- Anemia of chronic disease (ACD), anemia of (chronic) inflammation (A(C)I), and 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 and age)
  - Low transferrin saturation (<20%)?
  - Determine site of blood loss?
- 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, autoimmune disease, malignancy, chronic kidney disease (CKD), advanced age, heart failure . . .
- Mediators of hyperinflammation
  - Interleukins (e.g., IL-1 and IL-6) and tumor necrosis factor (TNF-alpha)
  - Hepcidin, CRP . . .
- Relative decrease in EPO production and blunted response to EPO
- Functional (relative) iron deficiency (trapping of iron in RES)
- Therapy
  - Treat underlying cause
  - ESAs ± iron?
  - Anti-hepcidin approaches

Hepcidin – regulator of iron hemostasis

Anemia secondary to chronic kidney 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. Third National Health and Nutrition Examination Survey (1988-1994). Estimates and 95% confidence intervals are demarcated.


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+ yr 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
  - Double-blind, placebo-controlled clinical trial
  - 80 community-dwelling, pre-frail or frail (Hopkins Frailty Index score 1 to 3) patients 70+ yr 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)
  - Double-blind randomized study on darbepoetin 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)


Anemia secondary to chronic kidney disease (CKD)

- ESAs are active 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
  - Indication for treatment: symptoms attributable to anemia, Hb <10g/dL
  - Hb target: maintain 10.0-11.5 g/dL; not >13g/dL
  - 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
  - Escalation of ESA doses in patients with poor ESA response should be avoided


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

Symptomatic anemia
- Supportive therapy including transfusions and iron chelation
- Lenalidomide
- EPO ≤500 U/L and/or low transfusion need (<2 U/month)
- EPO >500 U/L and/or high transfusion need
  - Vapreotide
  - [Epoetin alfa (Lenalidomide)]

Recommendations of the Austrian MDS Platform
- Hypoplastic MDS HLA-DR15
- SyA (MDS)


ESAs in anemia in elderly

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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 prospective1,2 or historical controls3
- ESAs even improve survival in treated patients2,3; however, improvement in prospectively randomized trials has so far not been shown1
- A predictive model exists (Nordic score)4
- Low IPSS-R, low serum EPO, and low serum ferritin are significantly associated with better erythroid response5
- Results of 2 prospective phase III trials will be presented at ASH 2014


Guidelines on ESAs in CIA

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>ASCO/ASH1</th>
<th>NCCN2</th>
<th>EORTC3</th>
<th>ESMO4</th>
<th>EORTC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>When to start</td>
<td>Hb ≤11 g/dL (clinical decision if Hb 10-11 g/dL); symptomatic patients’ target Hb should be around 12 g/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target range</td>
<td>Hb ≤11 g/dL (clinical decision if Hb 10-11 g/dL); symptomatic patients’ target Hb should be around 12 g/dL</td>
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<td></td>
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<tr>
<td>General</td>
<td>Iron deficiency should be corrected before ESA treatment</td>
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</table>


Potential new parameters in the classification of AE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, IL-6</td>
<td>Useful in the definition of ACD</td>
</tr>
<tr>
<td>Hepcidin (sHJV)</td>
<td>Gluysoprotein-growth factor that is the primary stimulus of erythropoiesis</td>
</tr>
<tr>
<td>Hepcidin</td>
<td>sauce plasma; produced in liver by negative regulator of intestinal iron absorption and iron release from RIS and extracellular; mutations causes primary hemochromatosis</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Possible risk factors (Iron overload, co-receptor of hemochromatosis)</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Increased expression of iron exporter, is regulated by hepcidin</td>
</tr>
<tr>
<td>Hepcidin (Cell bound)</td>
<td>Cytokine produced in iron overload, co-receptor of hemochromatosis, induces hepcidin production</td>
</tr>
<tr>
<td>Hepcidin (Transmembrane ferroxidase in enterocytes, transporting dietary iron into the cell)</td>
<td>A measure of adequacy of hepcidin levels relative to body iron stores</td>
</tr>
<tr>
<td>Hepcidin (Transport)</td>
<td>Supramolecular formation in enterocytes, transporting dietary iron into the circulation</td>
</tr>
</tbody>
</table>


Anemia of the elderly

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

<table>
<thead>
<tr>
<th>Type of anemia</th>
<th>Evidence</th>
<th>Guidelines</th>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease</td>
<td>++++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Anemia of chronic disease</td>
<td>+</td>
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<tr>
<td>Unexplained anemia</td>
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<tr>
<td>Myelodysplastic syndrome</td>
<td>++</td>
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<td>++</td>
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<tr>
<td>Chemotherapy-induced anemia</td>
<td>++</td>
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</table>

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, thromboembolic complications, flu-like illness, and headache have to be considered and discussed with patient.

Past, Present, and Future of Erythropoietin Use in Anemia in Older Adults

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

Lisbon, October 23, from 15:30 – 17:00

Reinhard STAUDER MD, MSc, Associate Professor
Department of Internal Medicine V (Hematology and Oncology)
Innsbruck Medical University
Anichstraße 35, 6020 Innsbruck, Austria
reinhard.stauder@i-med.ac.at

Panel Q&A session

Closing remarks

Matti Aapro

Web key & evaluation form

Please complete and return your evaluation form after the symposium to receive your complimentary Web key, containing the abstract and key slides from each presentation.