Anaemia, Neutropenia, Thrombocytopenia, Hemostasis and Cancer

Updated Anaemia Guidelines: ASH NICE ESMO

M. Aapro
Dr Aapro is a consultant for Amgen, BMS, Celgene, Eisai, Genomic Health, GSK, Helsinn, Hospira, JnJ Novartis, Merck, Merck Serono, Pfizer, Pierre Fabre, Roche, Sandoz, Teva, Vifor

and has received honoraria for lectures at symposia of Amgen, Bayer Schering, Cephalon, Eisai, Genomic Health, GSK, Helsinn, Hospira, Ipsen, JnJ OrthoBiotech, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Teva, Vifor

No responsibility accepted for involuntary errors or omissions. The list may be incomplete, and does not reflect consultancy for NGOs, Universities, Governmental agencies, and others.
EORTC Guidelines for Erythropoietic Proteins in Anaemic Patients with Cancer revisited

Review

EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update

C. Bokemeyer\textsuperscript{a},* M.S. Aapro\textsuperscript{b}, A. Courdi\textsuperscript{c}, J. Foubert\textsuperscript{d}, H. Link\textsuperscript{e}, A. Österborg\textsuperscript{f}, L. Repetto\textsuperscript{g}, P. Soubeyran\textsuperscript{h}

\textsuperscript{a}Universitätsklinikum Hamburg Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany
\textsuperscript{b}Institut Multidisciplinaire d'Oncologie, 1 route du Muids, CH-1272 Genolier, Switzerland
\textsuperscript{c}Radiotherapy Department, Centre Antoine-Lacassagne, 33 Av Vallombrose, 06189 Nice, Cedex 2, France
\textsuperscript{d}Erasmushogeschool, Departement Gezondheidszorg, Laarbeeklaan 121, 1090 Jette, Brussels, Belgium
\textsuperscript{e}Medizinische Klinik 1, Westpfalz-Klinikum, Hellmut Hartert Strasse 1, 67653 Kaiserslautern, Germany
\textsuperscript{f}Departments of Haematology and Oncology, Karolinska University Hospital, Stockholm, Sweden
\textsuperscript{g}Medical Oncology, Instituto Nazionale di Riposo e Cura per Anziani, Via Cassia 1167, Rome 00189, Italy
\textsuperscript{h}Institut Bergonié, 229 Cours de l'Argonne, F-33076 Bordeaux, France
clinical practice guidelines

Erythropoiesis-stimulating agents in the treatment of anaemia in cancer patients: ESMO Clinical Practice Guidelines for use

D. Schrijvers¹, H. De Samblanx¹ & F. Roila²
On behalf of the ESMO Guidelines Working Group*

¹Department Hemato-Oncology, Ziekenhuisnetwerk Antwerpen-Middelheim, Antwerp, Belgium; ²Department of Medical Oncology, Santa Maria Hospital, Terni, Italy
Erythropoiesis-Stimulating Agents—ESAs: The 2015 ESMO guidelines

ENTER YOUR NAME on behalf of Authors, et al

DRAFT

THIS DRAFT IS BASED ON THE 2014 SLIDE SET
Guidelines for Treatment of Anaemia in Patients with Cancer
The 2015 ESMO guidelines

ENTER YOUR NAME
on behalf of
Authors, et al
DRAFT

THIS DRAFT IS BASED ON THE 2014 SLIDE SET
The European Medicines Agency (EMEA) labels the use of ESAs as follows:

In patients treated with chemotherapy and an Hb level of <10 g/dl, treatment with ESAs might be considered to increase Hb to ≤ 12 g/dl or to prevent further decline in Hb [II, A].

In patients treated with curative intent, ESAs should be used with caution [D].

Treatment recommendations according to label can be followed if there is no suspicion of functional iron deficiency (ferritin >100 ng/ml and TFS saturation <20%).
Guidelines for Treatment of Anaemia in Patients with Cancer

“We confirm that QoL can be significantly improved in anaemic cancer patients following treatment of anaemia”

The two major goals of anaemia therapy are prevention of transfusions and improvement of QoL (grade A).

Cochrane meta-analysis on EPOs and QOL
Erythropoietin or darbepoetin for patients with cancer (Review)

Erythropoietin or darbepoetin for patients with cancer (Review)


Overall, there is a statistically significant difference between patients treated with ESAs and controls when combining QoL parameters and fatigue- and anaemia-related symptoms, which is however, most likely not clinically important.
Guidelines for Treatment of Anaemia in Patients with Cancer

- Additional causes of anaemia should be corrected prior to erythropoietic protein therapy
- ........ iron deficiency (absolute or functional), bleeding, vitamin B12 or folate deficiency, nutritional defects or haemolysis
Guidelines for Treatment of Anaemia in Patients with Cancer

Prevalence and management of cancer-related anaemia, iron deficiency and the specific role of i.v. iron

M. Aapro¹*, A. Österborg², P. Gascón³, H. Ludwig⁴ & Y. Beguin⁵

¹IMO Clinique de Genolier, Genolier, Switzerland; ²Department of Hematology, Karolinska Institute and Karolinska Hospital, Stockholm, Sweden; ³Department of Haematology-Oncology, Hospital Clinic de Barcelona, University of Barcelona, Barcelona, Spain; ⁴Department of Medicine i. Center for Oncology and Haematology, Wilhelminenspital, Vienna, Austria; ⁵Department of Medicine, Division of Hematology, University Hospital Liège, Liège, Belgium

Epidemiological and nonclinical studies investigating effects of iron in carcinogenesis—A critical review☆

Yves Beguin a,*, Matti Aapro b, Heinz Ludwig c, Lee Mizzen d, Anders Österborg e

a University Hospital Liège, Belgium 
b IMO Clinique de Genolier, Switzerland 
c Center for Oncology and Haematology, Wilhelminenspital, Vienna, Austria
d Vifor Pharma, Victoria, Canada
e Karolinska Institutet and Karolinska Hospital, Stockholm, Sweden
Accepted 31 October 2013
### Guidelines and Recommendations

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to ESA therapy</td>
<td>Baseline and periodic monitoring</td>
<td>Baseline and periodic monitoring</td>
<td>Baseline and prior ESA therapy</td>
<td>Prior to ESA therapy and before each chemotherapy cycle</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iron parameter</th>
<th>TSAT, sF</th>
<th>TSAT, sF</th>
<th>TSAT or sF</th>
<th>Not defined</th>
<th>TSAT or sF</th>
</tr>
</thead>
</table>

#### ID Definition

<table>
<thead>
<tr>
<th>AID: sF &lt;30 ng/mL, TSAT &lt;20%</th>
<th>Not defined</th>
<th>Not defined</th>
<th>FID: TSAT &lt;20%; ferritin ≥100* ng/mL</th>
<th>FID: high hepcidin; TSAT &lt;20%; ferritin ≥100 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>FID: sF 30-800 ng/mL, TSAT 20-50%</td>
<td>Not defined</td>
<td>Not defined</td>
<td>AID: Ferritin &lt;100* ng/mL; TSAT &lt;20%</td>
<td>AID: low hepcidin; Ferritin &lt;100 ng/mL; high hepcidin; TSAT &lt;20%</td>
</tr>
<tr>
<td>*in high CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Iron supplement

<table>
<thead>
<tr>
<th>AID: I.V. or oral iron</th>
<th>ID correction</th>
<th>In patients with IDA</th>
<th>ID correction</th>
<th>i.v. iron is superior to oral iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>FID: I.V. iron added to ESA</td>
<td>Consider I.V. iron to reduce ESA need, but not as standard of care</td>
<td>I.V. iron stated to increase Hb more than oral iron</td>
<td>AID &amp; FID: I.V. iron preferred</td>
<td>No response with oral iron in patients with active cancer and chemo</td>
</tr>
<tr>
<td>In various scenarios, I.V. iron mentioned as preferred route</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### I.V. iron dosing

| IS: 200mg Q2 - 3W* | FG: 8x 125 mg QW* | LMWID: 100 mg QW or TDI (*1000 mg total dose) | No dosing recommendation | No dosing recommendation | When possible 1000 mg maximum | No dosing recommendation |

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Guidelines for Treatment of Anaemia in Patients with Cancer

- Patients under chemotherapy whose Hb level is below 8 g/dL should be evaluated for need of transfusions, in addition to ESAs (if chemo) and iron.
There are no convincing studies indicating that patients treated in the curative setting with chemotherapy should be excluded from treatment with ESAs as per label, with any specific pathology.
Minireview

Effects of erythropoietin receptors and erythropoiesis-stimulating agents on disease progression in cancer

M Aapro*,1, W Jelkmann2, SN Constantinescu3 and B Leyland-Jones4

1Institut Multidisciplinaire d’Oncologie, Clinique de Genolier, Route du Muics 3, PO Box 100, Genolier CH-1272, Switzerland; 2Institute of Physiology, University of Lübeck, Ratzeburger Allee 160, Lübeck D-23538, Germany; 3Ludwig Institute for Cancer Research and de Duve Institute, Université Catholique de Louvain, Avenue Hippocrate 74, UCL 75-4, Brussels B-1200, Belgium; 4Winship Cancer Institute, Emory University, School of Medicine, 1365C Clifton Rd NE, Ste 4014, Atlanta, GA 30322, USA
Guidelines for Treatment of Anaemia in Patients with Cancer

MDS will be included in the recommendations
Guidelines for Treatment of Anaemia in Patients with Cancer

- Discussion of Tx risk

- Tx data are not at the level of registration for any drug
Guidelines for Treatment of Anaemia in Patients with Cancer

The target Hb concentration (Grade B) is about 12 g/dl
The target Hb concentration (Grade B) is about 12 g/dl

NO CHANGE…but point out some meta-analyses (darbo, epoetin beta) do not show an increased risk with an absolute higher level, but actually responding patients do better (darbo analysis). This limit is related to lack of data of symptom benefit and further transfusion avoidance above this Hb level.
Guidelines for Treatment of Anaemia in Patients with Cancer

When using erythropoietic proteins to treat anaemia in cancer patients, the combined analysis of all study data indicates an approximately 1.6-fold increased risk of thromboembolic events (grade A).
Guidelines for Treatment of Anaemia in Patients with Cancer

When using erythropoietic proteins to treat anaemia in cancer patients, the combined analysis of all study data indicates an approximately 1.6-fold increased risk of thromboembolic events (grade A).

List of risk factors and prevention of thrombo-embolic events
(LWMH use as per existing ESMO guidelines)
Guidelines for Treatment of Anaemia in Patients with Cancer

- USE THE AGENTS ACCORDING TO LABEL

  SPECIFIC SECTION ON BIOSIMILARS and ALL « EPOs »

  THAT ARE APPROVED BY EMA
## Recombinant erythropoietins approved in the EU

<table>
<thead>
<tr>
<th>Compound</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First generation</strong></td>
<td></td>
</tr>
<tr>
<td>Epoetin beta</td>
<td>NeoRecormon®</td>
</tr>
<tr>
<td>“Biosimilar epoetin alfa”</td>
<td>Epoetin alfa</td>
</tr>
<tr>
<td></td>
<td>Hexal® Abseamed® Binocrit®</td>
</tr>
<tr>
<td>Epoetin delta</td>
<td>Dynepo® ??</td>
</tr>
<tr>
<td>Epoetin zeta</td>
<td>Retacrit® Silapo®</td>
</tr>
<tr>
<td>Epoetin theta</td>
<td>Eporatio® Biopoin®</td>
</tr>
<tr>
<td><strong>Second generation</strong></td>
<td></td>
</tr>
<tr>
<td>Darbepoetin alfa</td>
<td>Aranesp®</td>
</tr>
<tr>
<td>Methoxy polyethylene glycol-epoetin beta</td>
<td>Mircera®</td>
</tr>
</tbody>
</table>

# ESA Treatment Recommendations

## Chemotherapy-induced anaemia

<table>
<thead>
<tr>
<th>Doses of ESAs according to ESMO and/or based on EMA label</th>
<th>Epoetin alpha zeta*1</th>
<th>Epoetin beta¹</th>
<th>Darbepoetin alpha¹</th>
<th>Epoetin theta²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial dose</strong></td>
<td>150 IU/kg sc tiw or 450 IU/kg qw</td>
<td>30,000 IU sc qw</td>
<td>2.25 mg/kg sc qw 500 mg (6.75 mg/kg) sc q3w</td>
<td>20,000 IU sc qw</td>
</tr>
<tr>
<td><strong>Dose increase</strong></td>
<td>300 IU/kg sc tiw</td>
<td>60,000 IU sc qw</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td><strong>Dose reduction</strong></td>
<td>If result achieved: 25-50%  If Hb&gt;12g/dl: 25-50%  If Hb rise &gt;2g/dl/4weeks: 25-50%</td>
<td>If result achieved: 25-50%  If Hb&gt;12g/dl: 25-50%  If Hb rise &gt;2g/dl/4weeks: 25-50%</td>
<td>If result achieved: 25-50%  If Hb&gt;12g/dl: 25-50%  If Hb rise &gt;2g/dl/4weeks: 25-50%</td>
<td></td>
</tr>
<tr>
<td><strong>Dose withholding</strong></td>
<td>If Hb&gt;13 g/dl until 12g/dl</td>
<td>If Hb&gt;13 g/dl until 12g/dl</td>
<td>If Hb&gt;13 g/dl until 12g/dl</td>
<td>If Hb&gt;13 g/dl until 12g/dl</td>
</tr>
</tbody>
</table>

sc, subcutaneous; tiw, thrice weekly; qw, once weekly; q3w, once every 3 weeks.

Guidelines for Treatment of Anaemia in Patients with Cancer

Correct causes of anaemia other than cancer

Normal Hb levels
- Prophylactic treatment not recommended

Symptomatic Hb 8-10 g/dL*
- Consider ESA/iron treatment

Asymptomatic Hb ≤ 11.9 g/dL
- Consider ESA/iron treatment according to individual factors
  - Including risk of worsening of anaemia
  - Treat to target about 12 g/dL
  - Individualise treatment to maintain target Hb with minimal amount of treatment

Hb <8 g/dL
- Evaluate for transfusion need and consider ESA/iron treatment according to individual factors

* 8-10: in some cases Tx is needed

ESA only if Hb < 10.0 or per country specific label
A NICE POSITION

Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (including review of TA142)

Issued: November 2014

NICE technology appraisal guidance 323

guidance.nice.org.uk/ta323
1 Guidance

This guidance replaces Epoetin alfa, epoetin beta and darbepeotin alfa for cancer treatment-induced anaemia (NICE technology appraisal guidance 142, issued in May 2008). The review of epoetin alfa, epoetin beta and darbepeotin alfa for cancer treatment-induced anaemia has resulted in a change in the guidance. See About this guidance for more information.

1.1 Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepeotin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

1.2 If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.
### Erythropoiesis-stimulating agents (ESAs)

<table>
<thead>
<tr>
<th>Indicated in asymptomatic anaemia</th>
<th>Oxford</th>
<th>LoE</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>In dose-dense / dose-escalated CT (iddETC)</td>
<td>1a</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>In the adjuvant setting</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>In the neoadjuvant/metastatic setting</td>
<td>1a</td>
<td>A</td>
<td>+/-</td>
</tr>
</tbody>
</table>

- **Indicated in symptomatic anaemia**
  - In the adjuvant setting
  - In the neoadjuvant/metastatic setting
  - Treatment and secondary prophylaxis of chemotherapy induced anemia (CIA)
  - Improvement of outcome (DFS, OS)
  - Treatment start at Hb-levels approaching < 10 g/dL
  - Target Hb 11–12 g/dL
  - Thromboembolic events are increased with ESAs
Guidelines for Treatment of Anaemia in Patients with Cancer

- Clinical trials have established that
  - Parenteral iron has improved ESA response and reduced ESA dose
  - IV iron alone has shown Hb response in cancer patients receiving chemotherapy
  - ESAs decrease transfusion needs
  - Hb levels are sustained on ESAs, not with intermittent transfusions
  - ESAs increase quality of life in patients with symptoms related to anemia
  - ESAs should be used within guidelines
  - In pts with CIA there is no convincing evidence for tumour progression or negative impact on survival