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

definition of anaemia
Anaemia is defined as a reduction of the haemoglobin (Hb) concentration, red-cell count or packed cell volume below normal levels.

Mild anaemia is defined as an Hb of ≤11.9 g/dl and ≥10 g/dl, moderate anaemia as an Hb of ≤9.9 and ≥8.0 g/dl and severe anaemia as an Hb of <8.0 g/dl.

prevalence and causes
Causes of anaemia in cancer patients might be patient- (e.g. haemoglobinopathies, thalassaemia, diminished nutritional status with deficiencies); disease- (bone marrow infiltration, bleeding, hypersplenism, haemolysis, anaemia of chronic disease) or treatment-related (extensive radiotherapy; bone marrow and renal toxicity secondary to chemotherapy; or drug-induced haemolysis).

anaemia in patients with non-haematological malignancies
Anaemia of cancer is present in 40% of patients with non-myeloid malignancies. It is mild in 30%, moderate in 9% and severe in 1%. Overall incidence of anaemia during chemoradiotherapy is 54% (mild 39%, moderate 14% and severe 1%). The incidence is highest in patients with lung (71%) or gynaecological cancer (65%) and increases with the number of chemotherapy cycles.

anaemia in patients with haematological malignancies
Anaemia can be present in myelodysplastic syndromes (incidence of 60–80%), all types of leukaemia (acutelymphoid; lymphoid or myeloid), in multiple myeloma and lymphoma (71.6% at diagnosis) as well as thalassaemia and sickle cell anaemia. It may also be due to chemotherapeutic treatment for haematological conditions, after autologous stem cell transplantation, or bone marrow failure states.

evaluation of anaemia in cancer patients

grading of anaemia
Treatment-related anaemia is graded according to the National Cancer Institute-Common Toxicity Criteria of Adverse Events (CTCAEv3) (Hb grade 0: within normal limits; grade 1: lower normal limit 10.0 g/dl; grade 2: 8.0 to <10.0 g/dl; grade 3: 6.5 to <8.0 g/dl; grade 4: <6.5 g/dl; grade 5: death).

evaluation of anaemia
Patients with anaemia should be evaluated by a thorough history with emphasis on medication use; a blood examination including the reticulocyte count, iron, transferring saturation (TFS) and ferritin levels, C-reactive protein, folate and vitamin B12 status and a peripheral blood smear and if indicated a bone marrow examination; by an assessment of occult blood loss in stool and urine; and by evaluation of the renal function [D].

Coombs testing should be considered in patients with chronic lymphocytic leukaemia, non-Hodgkin’s lymphoma and in patients with a history of autoimmune disease [D].

Endogenous erythropoietin (EPO) levels may be determined to predict response in patients with myelodysplasia [D].

All causes of anaemia should be taken into account and, if possible, corrected before the use of erythropoiesis-stimulating agents (ESAs) [B].

Anaemia has a negative impact on the quality of life (QoL) [I] and is an important factor in cancer-related fatigue [II]. It also constitutes a negative prognostic factor for overall survival in most types of cancer [I].

indications for the use of ESAs

patients with non-haematological malignancies
The indication of ESAs is the treatment of symptomatic chemotherapy-induced anaemia in adult patients with ...
non-myeloid malignancies. The aim is to prevent red 

blood cell transfusions (RBCTs) and their possible 

complications (iron overload, transmission of infection, 

immune suppression related to transfusions) and to improve 

health-related quality of life (HRQoL) by increasing the 

Hb level.

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 < 2 g/dl or to prevent further decline in Hb 
  [II, A].
- In patients not treated with chemotherapy, there is no 
  indication for the use of ESAs and there might be an 
  increased risk of death when ESAs are administered to 
  a target Hb of 12–14 g/dl [I, A].
- In patients treated with curative intent, ESAs should be used 
  with caution [D].

Treatment recommendations according to label are given in 
Table 1 and can be followed if there is no suspicion of 

functional iron deficiency (ferritin >100 ng/ml and TFS 

saturation <20%).

- If the Hb increase is at least 1 g/dl above baseline after 4 weeks 
  of treatment, the dose may remain the same or may be 
  decreased by 25%–50%.
- If the Hb increase is <1 g/dl above baseline, the dose of 
  selected ESA should be increased (Table 1). If after an 
  additional 4 weeks of therapy, the Hb has increased by ≥1 g/dl, 
  the dose may remain the same or may be decreased by 25%–50%.
- In the case of response, treatment with ESAs should be 
  discontinued 4 weeks after the end of chemotherapy.
- If the Hb increase is <1 g/dl above baseline after 8–9 weeks of 
  therapy, response to ESA therapy is unlikely and treatment 
  should be discontinued.
- If the Hb rises by >2 g/dl per 4 weeks or if the Hb exceeds 
  12 g/dl, the dose should be reduced by ~25%–50%.
- If the Hb exceeds 13 g/dl, therapy should be discontinued 
  until Hb falls below 12 g/dl and then re instituted at a dose 
  25% below the previous dose.

Treatment with ESAs in patients with chemotherapy-induced 
anaemia increases Hb levels with an overall weighted mean 

difference of 1.63 g/dl [95% confidence interval (CI) 1.46– 

1.80 g/dl] compared with controls [I]. ESAs also reduce 

significantly the relative risk of receiving RBCTs by 36% 
[relative risk (RR) 0.64, 95% CI 0.60–0.68]. Patients with 

solid tumours and patients who are on platinum-based 

chemotherapy seem to benefit more than patients with other 
tumour types and receiving other tumour therapies [I].

HRQoL as measured by different evaluation tools is 

improved by ESAs in some studies [II], although it is not 
clear how these results translate into utility gains.

Continuing ESAs treatment beyond 6–8 weeks in he absence 
of response defined as a rise in Hb <1–2 g/dl or no diminution 
of RBCT requirement is not beneficial [I, A]. The Hb level 

should not exceed 12 g/dl [II, B] and if Hb level is >12 g/dl 
dose adaptations should be made.

patients with haematological malignancies 

myelodysplastic syndromes. In patients with low-risk 

myelodysplastic syndromes based on bone marrow blast 

percentage, number of cytopenias and cytogenetic analysis, 

ESAs (± granulocyte-colony stimulating factor (G-CSF)) can 
be used to improve anaemia (off-label indication). In two 
small randomized studies, ESAs induced a significantly better 

Hb response rate (36.8%–42%) compared with placebo 
(0%–10.8%) [II]. Patients with a higher average baseline serum 

EPO level (>250 U/l) have a smaller Hb change [II] and 

a lower rate of Hb response (27.3%) than groups with a lower 

baseline serum EPO level (34.9%).

Treatment with ESAs should start at ~450 IU/kg/week for at 
least 8–10 weeks [B]. Predictors of response to ESAs include 
a normal karyotype, endogenous EPO levels <100–200 mU/ml 
and the refractory anaemia subtype.

bone marrow transplantation. Shortly after autologous 
transplantation there is a reduced response to EPO, although 
endogenous EPO is produced by the kidney in appropriately 
increased amounts. Later responsiveness of the transplanted 
marrow to EPO recovers and transfusion requirements 
decrease.

After an allogeneic transplantation, there is a faster response 
to EPO of the bone marrow. Thereafter, inflammatory 
cytokines, characteristic of graft-versus-host disease and 
immunosuppressive therapy cause not only a reduction in 
endogenous EPO production but also a diminished response to 
EPO. ESA therapy has been shown to be effective after 
allogeneic transplantation, although at somewhat higher doses 
of 75–200 IU/kg [B].

Table 1. Treatment recommendations according to label (EMEA)

<table>
<thead>
<tr>
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<th>Epoetin α</th>
<th>Epoetin β</th>
<th>Darbepoetin</th>
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<tbody>
<tr>
<td>Initial treatment</td>
<td>150 IU/kg s.c. t.i.w.</td>
<td>30 000 IU s.c. q.w.</td>
<td>2.25 μg/kg s.c. q.w.</td>
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<tr>
<td>Dose increase</td>
<td>450 IU/kg s.c. q.w.</td>
<td>60 000 IU s.c. q.w.</td>
<td>500 μg (6.75 μg/kg) s.c. q.3w</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>300 IU/kg s.c. t.i.w.</td>
<td>If result achieved: 25%–50%</td>
<td>If result achieved: 25%–50%</td>
</tr>
<tr>
<td>Dose witholding</td>
<td>If Hb &gt; 12 g/dl: 25%–50%</td>
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<tr>
<td>Dose withholding</td>
<td>If Hb &gt; 13 g/dl/4 weeks: 25%–50%</td>
<td>If Hb &gt; 13 g/dl/4 weeks: 25%–50%</td>
<td>If Hb &gt; 2 g/dl/4 weeks: 25%–50%</td>
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<td></td>
<td>If Hb &gt; 13 g/dl/4 weeks/4 week: 25%–50%</td>
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s.c.: subcutaneous; t.i.w., thrice weekly; q.w., once weekly; q.3w., once every 3 weeks.
comparison between ESAs

There is no difference between different ESAs in relation to effectiveness and safety [I].

recommendations in relation to iron

Baseline and periodic monitoring of iron, C-reactive protein, TFS and ferritin levels are necessary [D].

In anaemic patients with iron deficiency, intravenous iron supplementation leads to higher Hb increment in comparison with oral or no iron substitution [II, A].

Iron supplementation also appears to reduce the numbers of patients receiving RBCTs [I].

cancer therapy outcome

The influence of ESAs on tumour response and overall survival in anaemic cancer patients remains unclear. Several randomized trials have demonstrated decreased survival times and poorer locoregional control or progression-free survival but the design of these studies was aimed at Hb levels of >12 g/dl and included patients with a baseline Hb level of >11 g/dl [II].

In one meta-analysis, there was no effect on disease-free survival or disease progression in patients treated with chemotherapy in combination with darbepoetin [I].

Other recent meta-analyses showed that ESAs increased mortality [combined hazard ratio (cHR) 1.17, 95% CI 1.06–1.30; RR 1.15; 95% CI 1.03–1.29] and worsened overall survival (cHR 1.06, 95% CI 1.00–1.12) when given to cancer patients.

In all three meta-analyses, patients treated with chemotherapy had no increased mortality (HR 0.97, 95% CI 0.85–1.1; cHR 1.10, 95% CI 0.98–1.24; 1.04, 95% CI 0.86–1.26).

safety and tolerability

ESAs should not be used in patients with a known hypersensitivity to ESAs or any of the excipients and in patients with poorly controlled hypertension [B]. Their effect on patients with impaired liver function is unknown and they should be used with caution in patients with liver disease [D].

The relative risk of thromboembolic events is increased by 67% in patients treated with ESAs compared with placebo (RR 1.67; 95% CI 1.35–2.06) [I]. The use of ESAs should be carefully reconsidered in patients with a high risk of thromboembolic events such as a previous history of thrombosis, surgery, prolonged immobilization or limited activity and in patients with multiple myeloma and treated with thalidomide or lenalidomide in combination with doxorubicin and corticosteroids [D]. There are no data on the preventive use of anticoagulants or aspirin.

Pure red cell aplasia (PRCA) caused by neutralizing anti-erythropoietin antibodies has been observed in association with ESAs in patients with chronic renal failure [V], although no PRCA has been reported in cancer patients. This was likely due to manufacturing issues [II, B].

Other side-effects of ESAs are rare allergic reactions including dyspnoea, skin rash and urticaria; arthralgia; peripheral oedema; and mild and transient injection site pain [I].

pharmaco-economic considerations

Use of ESAs profoundly increases health care costs [I] and the cost per quality-adjusted life-year (QALY) is estimated to be €208 000 since there seems to be no survival benefit [II].

note

Levels of Evidence [I–IV] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the authors and the ESMO faculty.

literature


