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

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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 chemo- or radiotherapy 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 (acute-chronic; 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

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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 reinstituted 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 (≥500 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)

	Epoetin α	Epoetin β	Darbepoetin
Initial treatment	150 IU/kg s.c. t.i.w.	30 000 IU s.c. q.w.	2.25 μg/kg s.c. q.w.
	450 IU/kg s.c. q.w.		500 μg (6.75 μg/kg) s.c. q.3w
Dose increase	300 IU/kg s.c. t.i.w.	60 000 IU s.c. q.w.	Not recommended
Dose reduction	If result achieved: 25%–50%	If result achieved: 25%–50%	If result achieved: 25%–50%
	If Hb > 12 g/dl: 25%–50%	If Hb > 12 g/dl: 25%–50%	If Hb > 12 g/dl: 25%–50%
	If Hb rise > 2 g/dl/4 weeks: 25%–50%	If Hb rise > 2 g/dl/4 weeks: 25%–50%	If Hb rise > 2 g/dl/4 weeks: 25%–50%
Dose witholding	If Hb > 13 g/dl until 12 g/dl	If Hb > 13 g/dl until 12 g/dl	If Hb > 13 g/dl until 12 g/dl

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 darbepoietin [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.

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