New BSMO guidelines concerning anemia:

management of anemia and iron deficiency

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Background

Anemia and iron deficiency are frequent complications in patients with solid tumours or hematological malignancies, particularly in patients treated with chemotherapeutic agents.

Increased release of inflammatory cytokines due to the underlying cancer and toxicity of cancer therapy:
impaired erythropoietic activity and disturbed iron status.

Nutritional status with vitamin B12 and folate deficiency

Results in:

* fatigue
* impaired physical function
* reduced quality of life
* impaired response to cancer treatment
* reduced overall survival ?

Table 3 Severity-based grading systems (3,4)

Level	NCI (Hb, g/dL)	WHO (Hb, g/dL)	China (Hb, g/dL) (4)
Level 0 (normal)	Normal value*	≥11	Normal value*
Level 1 (mild)	10.0-normal value*	9.5-10.9	9.1 - normal value*
Level 2 (moderate)	8.0-10.0	8.0-9.4	6.1-9.0
Level 3 (severe)	6.5-7.9	6.5-7.9	3.1-6.0
Level (extremely severe)	<6.5	<6.5	<3.0

Note: *Male >12 g/dL and female >11 g/dL

The major aims of anemia management

* the reduction of fatigue

* improved QoL with the minimum invasive treatment

Anemia management consists of:

* erythropoiesis-stimulating agent (ESA)

* treatment of iron deficiency (ID)

* blood transfusion

Erythropoiesis-stimulating agent

Chemotherapy induced anemia:

1. patients who are not receiving chemotherapy should not use ESAs. (except use in myelodysplastic syndromes)
2. increase Hb level to reduce the need for RBC transfusions
3. improvement in anemia-related symptoms

Increased risk of VTE:

1. risk factors are high hematocrit, older age, prolonged immobilisation, malignant disease, major surgery, multiple trauma, a previous VTE and chronic heart failure.
2. tumour types (e.g. pancreatic cancer) and treatment regimens (e.g. treatment with ESAs and immunomodulatory drugs in multiple myeloma) are associated with an increased risk of VTE.
3. in the absence of prospective randomised studies showing that antithrombotic therapy reduces the risk of VTEs in ESA-treated patients, prophylactic antithrombotic treatment is not recommended.

Erythropoiesis-stimulating agent

ESAs might compromise tumor control and survival:

1. in all of these trials the target hemoglobin was high (> 12g/dl).
2. whether the use of ESAs should be restricted to patients receiving palliative rather than curative chemotherapy is controversial.
3. there is no clinical evidence indicating an effect of ESAs on stimulating disease progression or relapse when used within label and following recommendations for the treatment of CIA.

Iron deficiency

1. Iron deficiency: low transferrin saturation (TSAT < 20%)

   * absolute ID (depleted iron stores, serum ferritin < 30 ng/mL)
   * functional ID due to inflammation (adequate iron stores with increased serum ferritin)

2. I.v. iron supplementation (total doses of 1000mg of iron) significantly improved the hematological response to ESA treatment versus ESA alone.
3. The benefit of i.v. iron has significantly greater improvement of hematological response than with oral iron.
4. Administration of a single 1000 mg iron dose is more convenient for patients than multiple lower doses. Iron overload is unlikely in patients with CIA and is discussed for MDS patients
5. None of the trials investigating i.v. iron treatment together with ESAs showed an increased progression of tumours

Blood transfusion

- RBC transfusions are reserved for patients with severe anemia symptoms in need of rapid Hb improvement.
- Guidelines recommend transfusing only the minimum number of RBC units required to relieve severe anemia symptoms or to return the patient to a safe Hb range (e.g. 7–8 g/dL in stable, non-cardiac in-patients).
- There remains the risk of transmitting emerging pathogens and an increased risk of infections due to transfusion-related immunosuppression.
- Stressful for the patient, duration of transfusion, transfusion reactions and circulatory overload
- Whether a higher transfusion threshold may be warranted in patients with specific conditions (e.g. acute coronary syndrome) needs to be investigated.

Practical guidelines

- ESA is recommended in patients with symptomatic anemia who receive chemotherapy or combined radio-chemotherapy and present with an Hb level < 10 g/dL. (reimbursement Belgium Hb<11 g/dl, no curative setting)
- The target is a stable hb level of 12 g/dL without RBC transfusions: the dose should be adjusted to maintain the lowest Hb sufficient to avoid RBC transfusion
- Clinicians should carefully weigh the risk of thromboembolism in patients who are being considered for ESAs
- We recommend supplemental IV iron 1000mg as single dose for all patients with ESAs in case of functional ID or to correct absolute ID (reimbursement Belgium unclear)
- In patients with Hb < 7–8 g/dL and/or severe anemia-related symptoms (even at higher Hb levels) and the need for immediate Hb and symptom improvement, RBC transfusions are justified

Practical guidelines

- The starting doses and dose modifications of ESAs after response or nonresponse should follow the approved guidelines
- ESAs should be discontinued after 8 weeks in non-responders (< 1g/dl or no diminution of transfusion requirements)
- No evidence of differing efficacy among ESAs and no recommendation to change from one product to another in the case of an insufficient response.

Epoetin alpha (EPREX)	450 IU/kg subcutaneously once weekly or 150 IU/kg subcutaneously 3 times per week
Epoetin beta (NEORECORMON)	30 000 IU subcutaneously (i.e. ~ 450 IU/kg body weight in a 70 kg patient) given once weekly or divided over 3–7 times per week
Epoetin theta (EPORATIO)	20 000 IU subcutaneously independent of body weight given once weekly, dose may be doubled after 4 weeks if Hb has not increased by at least 1 g/dL
Epoetin zeta (RETACRIT)	450 IU/kg subcutaneously once weekly, or 150 IU/kg subcutaneously 3 times per week
Darbepoetin alpha (ARANESP)	500 µg (6.75 µg/kg body weight) subcutaneously given once every 3 weeks or 2.25 µg/kg body weight subcutaneously once weekly

Use in Myelodysplastic syndromes

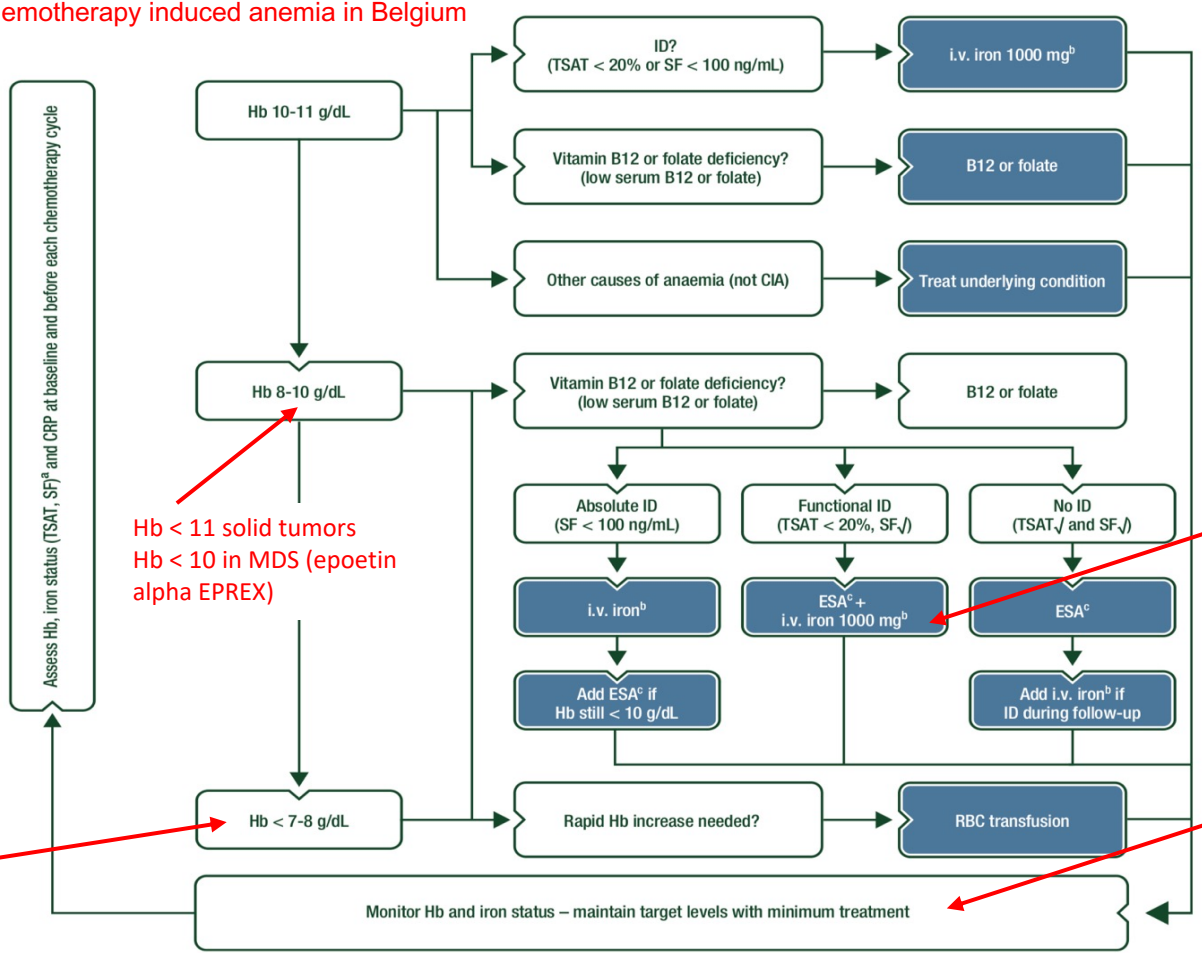
1. ESA should be considered for the treatment of symptomatic anemia (Hb ≤10 g/dL) with low or intermediate-1-risk MDS who have low serum erythropoietin (< 200 mU/mL). Not all ESAs are currently approved for use in patients with MDS (reimbursement Belgium Eprex hb ≤10 g/dl)

1. There is no evidence for a negative impact on survival or acute myeloid leukaemia evolution. There seems to be no association between the use of ESAs and thrombosis in patients with MDS.

2. Lenalidomide is recommended for patients with IPSS low/intermediate-1-risk 5qdeletion MDS without additional cytogenetic abnormalities and transfusion-dependent. Starting dose is 10 mg/day on day 1-21 of 28-day treatment cycles. Response to treatment should be evaluated after the fourth cycle.

3. Not all lower risk MDS patients with anemia will respond to ESA. This is largely due to the fact that these patients already have increased serum erythropoietin concentrations. Improving erythropoiesis can also be achieved by targeting downstream processes independent of erythropoietin regulation. Luspatercept is now reimbursed in this setting in Belgium.

Chemotherapy induced anemia in Belgium



Palliative setting

No ESA in curative setting ?

Hb < 11 solid tumors
Hb < 10 in MDS (epoetin alpha EPREX)

Reimbursement unclear

Target < 12 g/dL

Stop 4 weeks after chemo

Stop after 8 weeks in non responders

specific conditions with higher threshold ?

References:

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Mhaskar R, Wao H, Miladinovic B, et al. The role of iron in the management of chemotherapy-induced anemia in cancer patients receiving erythropoiesis-stimulating agents. Cochrane Database Syst Rev 2016; 2:CD009624

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