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CLINICAL PRACTICE GUIDELINES

Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines†

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Anaemia and iron deficiency (ID) are frequent complications in patients with solid tumours or haematological malignancies, particularly in patients treated with chemotherapeutic agents [1–3]. Frequently, anaemia is associated with fatigue, impaired physical function and reduced quality of life (QoL) [4–7]. Consequences of anaemia may include impaired response to cancer treatment and reduced overall survival (OS), even though a causal direct relationship has not yet been established [8, 9].

These new ESMO Clinical Practice Guidelines provide tools to evaluate anaemia, also in patients with myelodysplastic syndromes (MDS), and include recommendations on how to safely manage chemotherapy-induced anaemia (CIA) with erythropoiesis-stimulating agents (ESAs), iron preparations for intravenous (i.v.) or oral administration, red blood cell (RBC) transfusions and combinations of these treatments [10–13]. The major aims of anaemia management are the reduction or resolution of anaemia symptoms, particularly fatigue, and an improved QoL with the minimum invasive treatment that corrects the underlying causes and proves to be safe. Underlying causes of anaemia, mainly impaired erythropoietic activity and disturbed iron homeostasis, can be consequences of increased release of inflammatory cytokines due to the underlying cancer and/or toxicity of cancer therapy. Furthermore, vitamin B12 and folate deficiency are relatively rare causes of anaemia in cancer patients.

Notably, also more than half of patients with MDS are characterised by a haemoglobin (Hb) level < 10 g/dL, resulting in reduced functional capacities and health-related QoL, and $> 80\%$ of these patients require RBC transfusions [14–17]. However, ESAs were not approved by the European Medicines Agency (EMA) for use in MDS patients despite being used effectively in MDS for at least 20 years; their activity has been demonstrated in numerous clinical trials, with published evidence existing for more than 2500 ESA-treated MDS patients [14]. Randomised clinical trials are ongoing.

Since the publication of the European Society of Medical Oncology (ESMO) anaemia Clinical Practice Guidelines in 2010 [18] and the last review of the European Organisation for Research and Treatment of Cancer (EORTC) anaemia treatment guidelines in 2006 [19] (last update in 2007 [20]), clinical experience with ESAs and iron preparations and the understanding of iron homeostasis have markedly increased [10, 21]. Furthermore, specific safety aspects of the different treatment options have been addressed by several analyses and reviews in recent years, although data on the use of blood transfusions in cancer patients are sparse. Therefore, new ESMO guidelines for the diagnosis and treatment of anaemia and ID in cancer patients were deemed necessary. In addition, these guidelines include aspects related to anaemia management in patients with MDS and update the most recent ESMO and European LeukemiaNet (ELN) treatment guidelines for MDS [15, 22].

Questions addressed by these guidelines and respective recommendations including levels of evidence and grades of recommendations [23] are summarised in Table 1 for the management

Table 1. Managing anaemia and ID in patients with solid tumours or haematological malignancies

When should ESA treatment be considered?

Treatment of anaemia with an ESA should be considered in patients under ChT after correction of ID and other underlying causes other than the cancer or its treatment [I, A].

Which patients should receive ESA therapy?

ESA therapy is recommended in patients with symptomatic anaemia who receive ChT [I, A] or combined RT-ChT [II, B] and present with an Hb level < 10 g/dL, as well as patients with asymptomatic anaemia who receive ChT and present with an Hb level < 8 g/dL.

Should patients who do not receive ChT treatment be treated with an ESA?

ESA treatment is not recommended in patients who are not on ChT [I, A].

What is the Hb target range for treatment with an ESA?

The Hb target is a stable level of ~ 12 g/dL without RBC transfusions [I, A].

At what doses should ESAs be given?

Dosing should follow the approved labels of the individual products; the currently recommended dosage is approximately 450 IU/week/kg body weight for epoetins alpha, beta and zeta; 6.75 μg/kg body weight every 3 weeks or 2.25 μg/kg body weight weekly for darbepoetin alpha; and 20 000 IU once weekly for epoetin theta [I, A].

Should ESA doses be increased or ESA preparations changed in patients not responding within 4–8 weeks?

Except for patients receiving epoetin theta (given at an intentionally low starting dose), ESA dose escalations and changes from one ESA to another in patients not responding within 4–8 weeks are not recommended. Patients who do not show evidence of at least an initial Hb response at this time should stop ESA therapy. The epoetin theta dose may be doubled after 4 weeks if Hb has not increased by at least 1 g/dL, unless functional ID is detected (see next recommendation) [I, A].

Which patients should receive iron therapy?

Patients receiving ongoing ChT who present with anaemia (Hb ≤ 11 g/dL or Hb decrease ≥ 2 g/dL from a baseline level ≤ 12 g/dL) and absolute ID (serum ferritin < 100 ng/mL) should receive iron treatment with an i.v. iron preparation to correct ID. If ESA treatment is considered, iron treatment should be given before the initiation of and/or during ESA therapy in the case of functional ID (TSAT $< 20\%$ and serum ferritin > 100 ng/mL) [I, A].

Should patients receive i.v. iron therapy without an ESA?

i.v. iron without additional anaemia therapy may be considered in individual patients with functional ID (TSAT $< 20\%$ and serum ferritin > 100 ng/mL) [III, C].

Should patients who are not on ChT receive iron therapy?

Iron treatment should be limited to patients on ChT. In patients receiving cardiotoxic ChT, i.v. iron should either be given before or after (not on the same day) administration of ChT or at the end of a treatment cycle [III, C].

At what doses should i.v. iron be given?

Patients with confirmed functional ID should receive a dose of 1000 mg iron given as single dose or multiple doses according to the label of available i.v. iron formulations. Patients with confirmed absolute ID should receive i.v. iron doses according to the approved labels of available products until correction of ID [I, A].

Which patients should be considered for RBC transfusions?

In patients with Hb < 7–8 g/dL and/or severe anaemia-related symptoms (even at higher Hb levels) and the need for immediate Hb and symptom improvement, the administration of RBC transfusions without delay is justified [II, B].

ChT, chemotherapy; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; ID, iron deficiency; i.v., intravenous; RBC, red blood cell; RT, radiotherapy; TSAT, transferrin saturation.

of anaemia and ID in patients with solid tumours or haematological malignancies and in Table 2 for the management of MDS. These recommendations are further illustrated in treatment algorithms (Figures 1 and 2). Discussions of specific aspects underlying the recommendations and related to the different treatment options are summarised in this article.

Anaemia management in patient populations with solid tumours or haematological malignancies

ESAs

ESAs have been shown to increase Hb levels and to reduce the need for RBC transfusions in cancer patients receiving chemotherapy [24–27] and are approved for the treatment of CIA since 1993 [28]. Furthermore, a meta-analysis of 23 studies that reported QoL results and included 5584 patients showed a statistically significant difference between patients treated with ESAs and controls when combining QoL parameters and fatigue-related symptoms well as anaemia-related symptoms [29] (Table 3). However, the authors considered this finding to be not clinically important. Conversely, experience with patients responding to therapy and a recently published meta-analysis of 37 randomised, controlled trials with 10 581 patients suggest a small but clinically important improvement in anaemia-related symptoms [30].

Since early dose finding studies with epoetin beta did not show a difference in Hb response to 5000 and 10 000 IU/day (corresponding to 500 and 1000 IU/kg/week in a 70 kg individual) [31], and since there is not a single study on dose escalations showing a benefit, dose escalations in patients who do not respond within 4–8 weeks are not recommended (except for epoetin theta's

Table 2. Managing anaemia in patients with MDS

When should ESA treatment be considered?[a]

Treatment of anaemia with an ESA should be considered in MDS patients with symptomatic anaemia, Hb < 10 g/dL, low to intermediate-1 risk (IPSS) or very low to intermediate risk (IPSS-R), less than two RBC transfusions per month and/or serum EPO < 500 IU/L [I, A].

At what doses should ESAs be given?

ESAs should be given as fixed-dose, weekly, subcutaneous treatment at an initial dose in the range of 30 000–80 000 IU recombinant human EPO (epoetin theta starting dose is 20 000 IU) or up to 300 μg darbepoetin alpha [I, A].

How should MDS patients who are not responding to ESA treatment be treated?

In patients not responding to ESA treatment after 8–12 weeks, G-CSF should be added at ∼300 μg/week, given in 2–3 doses. RBC transfusions or investigational medicinal products should be considered as second-line treatment in patients without a 5q deletion, and lenalidomide in patients who acquired a 5q deletion [I, A].

How should transfusion-dependent, anaemic MDS patients be treated?

Patients who require 2 or more RBC transfusions per month should be considered for treatment with an investigational agent or supportive care with RBC transfusions if they have no 5q deletion, or for lenalidomide if they have a 5q deletion [I, A].

[a]ESAs are not all EMA-approved for use in patients with MDS. Epoetin alpha is indicated by the EMA for the treatment of symptomatic anaemia (haemoglobin concentration of ≤ 10 g/dL) in adults with low or intermediate-1 risk primary MDS who have low serum EPO (<200 IU/mL).

EMA, European Medicines Agency; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hb, haemoglobin; IPSS, International Prognostic Scoring System; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; RBC, red blood cell.

low starting dose to be doubled after 4 weeks if Hb response is < 1 g/dL). Instead, ESA treatment should be stopped at this time point if there is no emerging sign of Hb response. There is no evidence of differing efficacy among ESAs (Table 4) and no recommendation can be made to change from one product to another in the case of an insufficient response. Because of possible safety issues, we continue to recommend that products should not be used interchangeably without adequate traceability and without notifying the treating physician [V, C].

Are ESAs linked to mortality and tumour progression?

In the late 2000s, the safety of ESAs was discussed when meta-analyses suggested that ESA treatment may affect mortality in cancer patients [32, 33], particularly if target Hb levels exceeded 12 g/dL [34–38]. Consequently, the recommended Hb target range for ESA treatment is 10–12 g/dL, and an Hb rise of > 2 g/dL over a 4-week period should be avoided. In 2014, a study in anaemic patients with metastatic breast cancer suggested that addition of erythropoietin (EPO) to standard of care with a target Hb > 12 g/dL did not meet the non-inferiority criteria for progression-free survival (PFS) versus standard of care alone [39]. However, the late separation of the PFS and OS curves can hardly be explained by a few weeks of EPO exposure. Notably, the most recent Cochrane review included subgroup analyses and showed statistically significant on-study mortality in patients with baseline Hb > 12 g/dL but not for Hb categories Hb < 10 g/dL and Hb = 10–12 g/dL that correspond to the currently approved cut-off for initiation and the target Hb range of ESA therapy [29]. When excluding one study with a target Hb range above the labelled guidance (BEST, target Hb = 12–14 g/dL [36]), the effect lost statistical significance [odds ratio; 95% confidence interval (CI): 1.09 (0.97–1.23)]. Data from large studies [40–42] and other meta-analyses [43–47] that have been reported since the label change did not indicate an effect of ESAs on risk of disease progression. A retrospective analysis of 47 342 chemotherapy-treated patients from the SEER-Medicare database (years 1991–2002, including 12 522 ESA-treated patients) showed similar OS with or without ESA [48]. In November 2014, these data led the National Institute for Care and Health Excellence (NICE) in the UK to indicate that ESAs (epoetin alpha, beta, theta and zeta and darbepoetin alpha) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are receiving chemotherapy. If different ESAs are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used [49]. Overall, there is currently no clinical evidence (neither single studies nor meta-analyses) indicating an effect of ESAs on stimulating disease progression or relapse when used within label and following recommendations for the treatment of CIA [I, A] [29].

EPO receptor and tumour growth

Some reports suggested a potential role of the EPO receptor (EpoR) on tumour cells in tumour progression [50–52], yet there has been a controversial discussion about whether the tests for EpoR expression were specific enough [53] and about whether the functionality of detected EpoR (e.g. STAT5 activation [54]) was checked sufficiently [55–58]. In particular, the first publications suggesting EpoR expression in cancer cell lines used a polyclonal antibody [53], whereas more recent publications used a monoclonal (more specific) antibody against EpoR and failed to show such a receptor [57, 59]. Results showing that EPO may antagonise anti-HER2 therapy in breast cancer via Jak2-mediated signalling [60] suggest further investigation of this pathway. In recent *in vitro* studies, EpoR knockdown decreased proliferation of different tumour cell lines [61, 62], yet many tumour cell lines and primary renal cancer cells express constitutively phosphorylated (active) EpoR [63]. In animal tumour models, EPO did not enhance proliferation of tumour cell lines or affect mortality [52, 64].

ESAs and risk and prophylaxis (prevention) of thromboembolic events

Venous thromboembolic events (VTEs) are a known risk of ESA use in cancer patients [45], and the risk of a VTE is increased

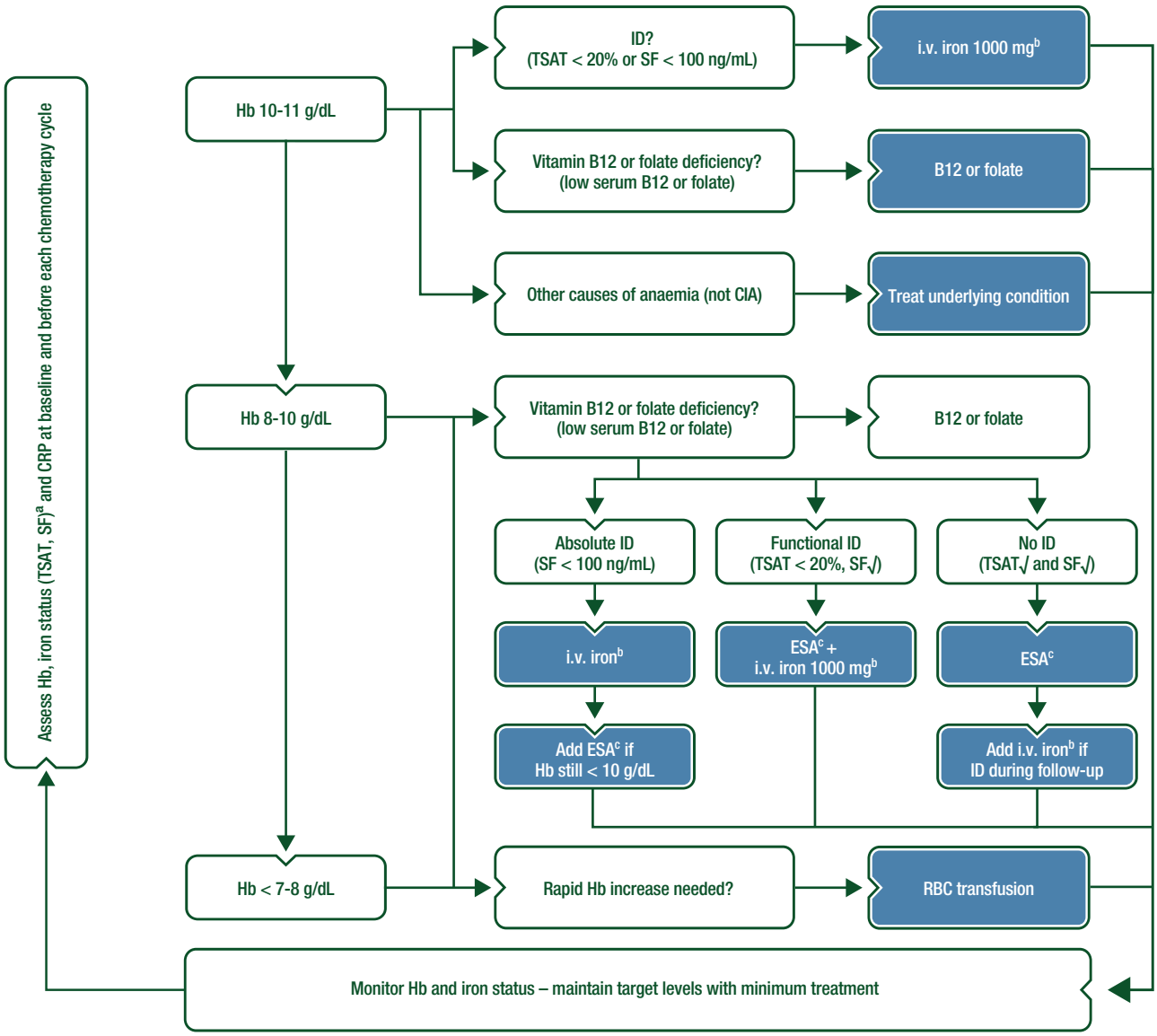

Figure 1. Management of chemotherapy-induced anaemia in patients with solid or haematological malignancies.
[a]Other parameters for impaired iron status: % hypochromic cells (%HYPO) > 5% and Hb content of reticulocytes (CHr) < 28 pg.
[b]i.v. iron given as a single dose of 1000 mg iron or an equivalent total dose in several infusions as feasible with available i.v. iron formulations. Oral iron to be considered only for patients with ferritin < 30 ng/mL and non-inflammatory conditions [CRP < 5 mg/L].
[c]ESA dosing should follow approved labels (i.e. ∼450 IU/week/kg body weight for epoetins alpha, beta and zeta; 6.75 μg/kg body weight every 3 weeks or 2.25 μg/kg body weight weekly for darbepoetin alpha; 20 000 IU once weekly for epoetin theta which may be doubled after 4 weeks upon insufficient response). ESA dose escalations or a change to another ESA in patients who do not respond within 4–8 weeks are not recommended; ESA should be stopped in this case.
√, normal; CIA, chemotherapy-induced anaemia; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; ID, iron deficiency; i.v., intravenous; RBC, red blood cell; SF, serum ferritin; TSAT, transferrin saturation.

1.5-fold. The most important risk factors of a VTE are high haematocrit, older age, prolonged immobilisation, malignant disease, major surgery, multiple trauma, a previous VTE and chronic heart failure [43]. In addition, tumour types (e.g. pancreatic cancer) and treatment regimens (e.g. treatment with ESAs and/or immunomodulatory drugs in multiple myeloma) are associated with an increased risk of VTE [65, 66]. Clinical evidence on whether ESA treatment further increases the risk of VTEs when added to immunomodulatory treatments lenalidomide or thalidomide in patients with multiple myeloma is not conclusive and may depend on the treatments used or the study design [67, 68]. 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 and the ESMO guidelines on VTEs should be followed [69]. Other guidelines in the field are issued by the National Comprehensive Cancer Network (NCCN) [70] and the American Society of Clinical Oncology (ASCO) [71]. Notably, VTEs may be in part associated with thrombocytosis, which correlates with ID that can occur due to the rapid consumption of available iron by

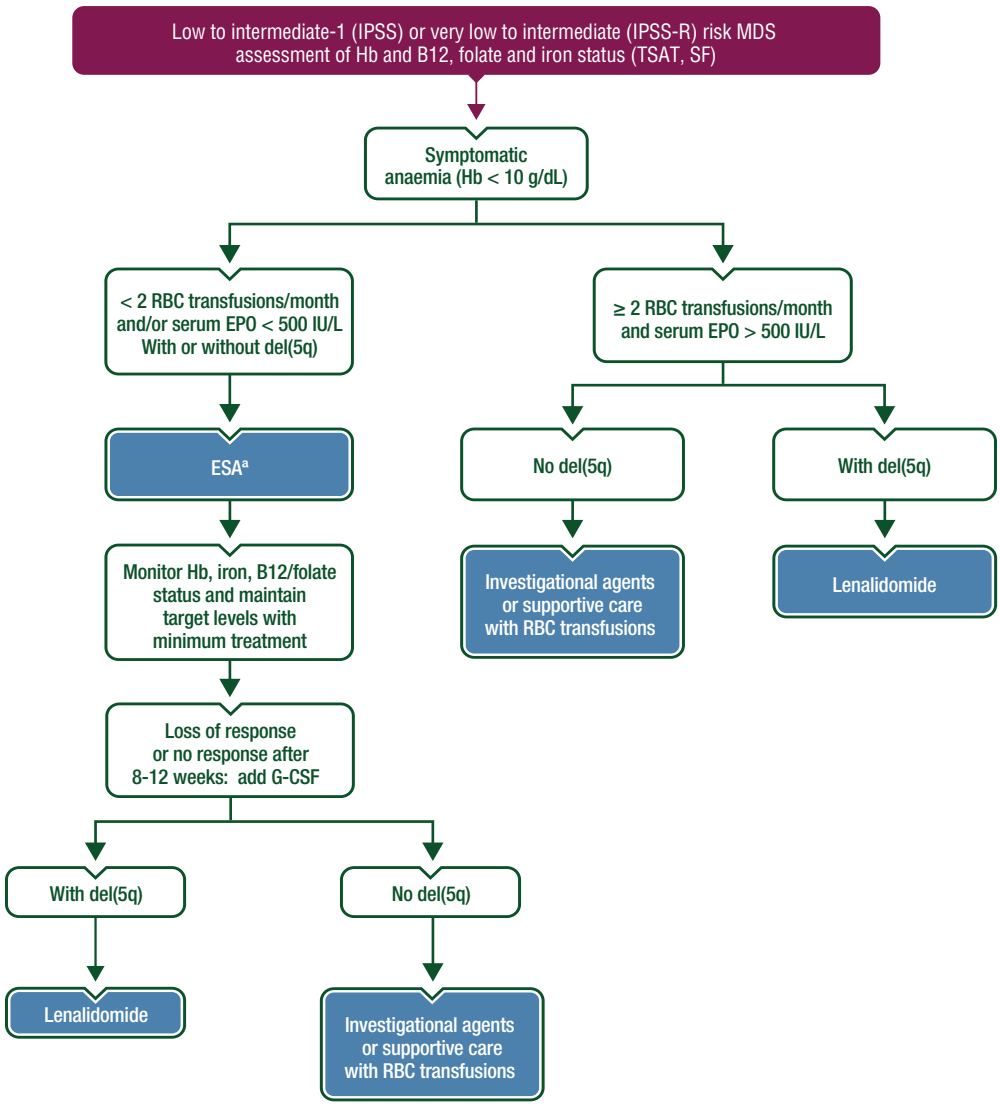

Figure 2. Management of anaemia in patients with very low to intermediate-risk MDS.
[a]ESA-treated patients who are iron deficient and transfusion independent may be considered for i.v. iron treatment.
EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hb, haemoglobin; IPSS, International Prognostic Scoring System; IPSS-R, revised International Prognostic Scoring System; i.v., intravenous; MDS, myelodysplastic syndrome; RBC, red blood cell; SF, serum ferritin; TSAT, transferrin saturation.
Adapted from [22].

the increased RBC synthesis after ESA treatment, but this remains to be further investigated [72, 73]. Overall, individual risks and harms should be balanced and discussed with the patient [V].

ID in patients with solid or haematological malignancies

ID is defined by insufficient iron availability for cellular functions, the most prominent being haem synthesis for erythropoiesis [74]. Absolute ID refers to depleted iron stores, whereas functional ID reflects insufficient availability of iron despite filled iron stores; this may be due to either iron sequestration in iron stores or increased iron needs during erythropoietic therapy [10, 75, 76]. In cancer patients, absolute ID is due mainly to bleeding, while other causes such as insufficient intestinal iron resorption, e.g. due to poor nutrition, are usually of minor importance. Most importantly, iron homeostasis in cancer patients is often impaired via the release of proinflammatory cytokines and upregulation of hepcidin, the main regulator of iron uptake and release [76]. Increased hepcidin levels result in insufficient iron supply and functional ID due to internalisation of ferroportin, the most important transmembrane channel for the export of iron from enterocytes and macrophages into the circulation.

In 2006, the EORTC recommended iron treatment for the correction of ID before the initiation of ESA therapy [19] and recommended the use i.v. iron in patients with absolute or functional ID in the 2007 guideline update [20]. However, no details on iron status assessment or iron dosing were given due to limited evidence at that time.

Table 3. Benefit-risk profiles of treatments for anaemia and ID in cancer patients

	Benefits	Risks or limitations
ESAs	• Reduction of RBC transfusions • Improvement in anaemia-related symptoms	• Increase in thrombotic events • PRCA in rare cases[a] • Increased mortality in patients receiving no cancer therapy or only RT • Only effective in 60% of patients • Induction of functional ID and decreasing response over time
i.v. iron[b]	• Correction of ID anaemia • Reduction of RBC transfusions • Increase response to ESAs	• Long-term safety in oncology not yet fully established
RBC transfusions	• Immediate increase of Hb and haematocrit levels in 100% • Rapid improvement in anaemia-related symptoms	• Increase in thrombotic events • Transfusion reactions and circulatory overload • Transmission of known/unknown pathogens • Possibly decreased survival in certain types of cancer treated by surgery • Increased risk of infections due to immunosuppression

[a]Documented only in non-cancer chronic kidney disease patients.
[b]Oral iron to be considered only for patients with both absolute ID (ferritin < 100 ng/mL) and non-inflammatory conditions (CRP < 5 mg/L).
CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; ID, iron deficiency; i.v., intravenous; PRCA, pure red cell aplasia; RBC, red blood cell; RT, radiotherapy.

Table 4. Approved ESAs and i.v. iron compounds and their approved dosing in patients with solid tumours and haematological malignancies[a,b]

ESAs	
Epoetin alpha	450 IU/kg subcutaneously once weekly or 150 IU/kg subcutaneously 3 times per week
Epoetin beta	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	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	450 IU/kg subcutaneously once weekly, or 150 IU/kg subcutaneously 3 times per week
Darbepoetin alpha	500 μg (6.75 μg/kg body weight) subcutaneously given once every 3 weeks or 2.25 μg/kg body weight subcutaneously once weekly
i.v. iron[c]	
Ferric gluconate	Maximum infusion dose: 125 mg iron Minimum infusion time: 60 min
Iron sucrose	Maximum infusion dose: 200–500 mg iron Minimum infusion time: 30–210 min
Iron dextran[d]	Maximum infusion dose: depends on exact iron dextran type; refer to label. Minimum infusion time: 240–360 min
Iron isomaltoside	Maximum infusion dose: 20 mg/kg body weight (up to 1000 mg iron[e]) Minimum infusion time: 15 min[f]
Ferric carboxymaltose	Maximum infusion dose: 20 mg/kg body weight (up to 1000 mg iron per week) Minimum infusion time: 15 min

[a]Epoetin alpha is EMA-approved for low or intermediate-1 risk MDS (see text).
[b]Both originator products and biosimilars approved by the EMA have been shown to have similar safety and therapeutic equivalence in clinical practice.
[c]Follow the label indications in your country.
[d]Low molecular weight iron dextran.
[e]The authors suggest a dose up to 1000 mg, while drug labels might allow more.
[f]If dose is up to 1000 mg; if dose exceeds 1000 mg iron, more than 30 min is recommended, as per label.
EMA, European Medicines Agency; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; i.v., intravenous; MDS, myelodysplastic syndrome.

Iron status assessment

ID is reflected by a low transferrin saturation (TSAT < 20%) and can be further characterised as absolute ID (depleted iron stores, serum ferritin < 30 ng/mL) or functional ID (adequate iron stores with normal or increased serum ferritin) [10]. Although investigation of bone marrow iron stores is still considered standard, circulating ferritin levels are used for distinguishing between absolute and functional ID in clinical practice. In non-inflammatory conditions, a serum ferritin level < 30 ng/mL is indicative of absolute ID,

while higher levels usually reflect appropriate iron stores. However, in cancer and other conditions with an activated inflammatory cascade, ferritin follows the path of inflammatory cytokines. Hence, the cut-off levels should be raised to 100 ng/mL in patients with inflammation or cancer. Other biological markers of ID include hypochromic, microcytic red cells, a low cellular Hb content in reticulocytes (CHr < 28 pg) and an increased percentage of hypochromic RBCs (%HYPO > 5%) as markers of both absolute and functional ID [10, 77]. Levels of soluble transferrin receptor (sTfR) and zinc protoporphyrin are increased in patients with absolute ID, but sTfR value is usually within normal limits or low in functional ID except that observed with ESA treatment [10, 78, 79]. Notably, sTfR levels can be decreased after chemotherapy [80], whereas they are increased in patients with increased erythropoietic activity (or ESA treatment) and concomitant chemotherapy, limiting the relevance of sTfR as an indicator of iron status.

Clinical evidence for treatment with i.v. iron

In controlled clinical trials investigating iron supplementation in ESA-treated anaemic cancer patients, i.v. iron supplementation (total doses in the range of 1000 mg of iron) significantly improved the haematological response to ESA treatment versus ESA alone [81–86] (Table 3). Individual studies also showed additional benefits of i.v. iron such as improvement of QoL [81] reduction of RBC transfusions [83] and ESA doses [84]. One study showed no improvement with i.v. iron and reported a higher rate of adverse events in the experimental arm with i.v. iron, but this study used an unusual (off-label) iron dosing schedule and was terminated early [87, 88]. In contrast to i.v. iron treatment, therapy with oral iron did not result in better outcomes compared with control arms with no iron at all. Conversely, the benefits of i.v. iron were substantial, with significantly greater improvement of haematological response rate than with oral iron [81, 85]. Total dose infusion of calculated iron needs was as effective as multiple low-dose infusions [81], yet, depending on the individual i.v. iron product's approved maximum infusion dose (Table 4), administration of a single 1000 mg iron dose may be more convenient for patients than multiple lower doses. Iron overload is unlikely in patients with CIA and is discussed for MDS patients.

Earlier published studies in patients with gynaecological cancer [89, 90] or with lymphoid malignancies [91] and prospective observational studies [92, 93] have shown that some patients benefit from i.v. iron even without concomitant ESA (increase in Hb concentration, reduction of RBC transfusion need), but this remains to be confirmed in larger, randomised trials. Although a trial of i.v. iron alone may be considered in individual patients with functional ID, this approach cannot be recommended based on currently available data [III, C].

With i.v. iron, no increased risk of infection or cardiovascular morbidity has been observed [81–86]. However, i.v. iron should not be given to patients with an active infection. Concomitant administration of i.v. iron and cardiotoxic chemotherapy should be avoided, and i.v. iron should either be given before or after administration of chemotherapy or at the end of a treatment cycle [III, C]. The EMA no longer recommends administration of a test dose to predict/prevent allergic reactions (mainly observed with iron dextrans [94]); however, the EMA recommends that i.v. iron should only be administered by staff trained to evaluate and manage anaphylactic and anaphylactoid reactions and only when resuscitation facilities are immediately available. Patients should be observed closely for symptoms of hypersensitivity reactions for at least 30 min following each i.v. iron administration [95].

Is iron linked to tumour progression?

None of the trials investigating i.v. iron treatment together with ESAs showed an induction or increased progression of tumours [81–86]; however, the observation periods of these trials were rather short and there is uncertainty about potential late effects of iron treatment in cancer patients. One prospective, randomised, controlled study with longer follow-up that included treatment arms with and without i.v. iron administration in a limited number of patients with lymphoid malignancies and autologous haematopoietic stem cell transplantation showed no negative effect of i.v. iron on PFS (median follow-up 1.4 years, range of 89 days to 9.5 years) [96]. Results of available epidemiological and non-clinical studies are often conflicting and most experimental designs used intramuscular or intraperitoneal administration, high local iron concentrations and/or non-clinical iron preparations such as ferric nitrilotriacetate that do not reflect the clinical setting of iron-deficient cancer patients who receive approved i.v. iron preparations for Hb normalisation [97, 98]. When side-effects of iron are observed, they are most likely related to high loads of labile (non-transferrin-bound) iron, which catalyses the production of reactive oxygen species that lead to oxidative damage of cellular components including DNA [99, 100]. Hepatocyte iron overload with cirrhosis, as seen in hereditary haemochromatosis, has an established link to the development of hepatic cancer [101] and there seems to be a link between high dietary iron intake and colorectal cancer [102]. Notably, models that investigated iron as a potential promotor of tumour growth showed no effect of iron alone [103]. Some animal studies suggested that tumour progression occurs if large amounts of iron are given [104]; however, there is currently no clinical evidence for such an effect. This issue has not been specifically studied except in one study [96] and should be thoroughly investigated.

RBC transfusions

RBC transfusions have a long history of use with benefit to patients who present with severe anaemia symptoms or bleeding conditions and require a rapid increase in Hb and haematocrit to normal laboratory values. The literature about RBC transfusions in the cancer population is primarily derived from patients undergoing surgery. The available literature on patients receiving chemotherapy is sparse and no randomised trials have compared the value of RBC transfusions in these patients or compared the use of ESAs with RBC transfusions. Patients with non-life-threatening, cancer-related anaemia and CIA often receive RBC blood transfusions as routine treatment [105, 106], in spite of limited evidence for a significant treatment effect [107, 108] unless the underlying conditions are corrected.

Advances in molecular testing for known pathogens and potential donor-recipient incompatibilities have improved the general safety of RBC transfusions over time. Nevertheless, there remains the risk of transmitting unknown or emerging pathogens before the development and implementation of effective tests (Table 3) and an increased risk of infections due to transfusion-related immunosuppression [109]. Furthermore, stored allogeneic blood can elicit prothrombotic as well as inflammatory responses (referred to as 'storage lesion') [110–112]. In the oncology surgery setting, large population-based studies and a meta-analysis suggest independent associations between RBC transfusions and an increased risk of mortality, morbidity and cancer recurrence, respectively [113–116]. Meta-analyses of studies comparing restrictive versus liberal RBC transfusion thresholds, mainly in patients with orthopaedic, cardiovascular or bleeding conditions, showed significant reductions in the proportions of transfused patients and the numbers of transfused RBC units without negative impact on mortality, morbidity and functional outcome [117–120]. Analysis of studies with a restrictive Hb threshold < 7 g/dL showed significant reductions in total and in-hospital mortality, rebleeding, acute coronary syndrome, pulmonary oedema and bacterial infections with a restrictive approach, compared with a more liberal strategy [118]. Whether a higher transfusion threshold may be warranted in patients with specific conditions (e.g. acute coronary syndrome) [121] needs to be investigated. In the oncology setting, the American Society of Hematology's Choosing Wisely® campaign and other societies' anaemia treatment guidelines recommend transfusing only the minimum number of RBC units required to relieve severe anaemia symptoms or to return the patient to a safe Hb range (e.g. 7–8 g/dL in stable, non-cardiac in-patients) [11, 13, 122, 123].

It is recommended that RBC transfusions are reserved primarily for patients with severe anaemia symptoms in need of rapid Hb improvement [II, B]. The concept of taking every reasonable measure to increase and maintain the patient's endogenous RBC mass early on and to protect it throughout the entire treatment, thus pre-empting transfusion, was developed in a non-oncology population and is called 'patient blood management' (PBM). It is based on three pillars, namely 1) optimising the patient's own red cell mass, 2) minimising blood loss and bleeding and 3) evaluating the physiological tolerance of anaemia. It should be accompanied by a concomitant, comprehensive assessment of a patient's haematological status at initial presentation and throughout therapy. PBM has been already well-established in the field of elective orthopaedic surgery and with the Australian National Blood Authority [124–126]. A detailed review of studies that evaluated the impact of transfusions on patient outcomes (including ischaemic events as the second leading cause of death in cancer patients [127]) is warranted but is beyond the scope of these guidelines.

Anaemia management in patients with MDS

Notably, the management of MDS-associated anaemia differs for several aspects from the above recommendations for solid tumours or other haematological malignancies such as multiple myeloma or lymphomas. In 2017 the EMA-approved ESA label of epoetin alpha (summary of product characteristics) includes treatment of some patients with MDS. Based on available data and published predictive scores [128, 129], these anaemia treatment guidelines (Table 1 and Figure 2) and other international as well as national MDS treatment guidelines [15, 22, 130–132] have included recommendations on the use of ESAs for the management of MDS-associated anaemia, and several countries have allowed and have reimbursed ESAs in this setting. The use of investigational treatments (suggested as second-line treatment) that are currently tested in clinical trials is discussed in more detail in the ESMO Clinical Practice Guidelines for MDS [22].

Many MDS patients present with normal or even increased iron stores due to ineffective erythropoiesis plus regular RBC transfusions and require iron chelation to reduce iron overload. Other risks and limitations of RBC transfusions that are not specific to MDS are discussed in the separate section 'RBC transfusions' above.

Clinical evidence for use of ESAs in MDS

Three meta-analyses evaluated the efficacy of recombinant human EPO (rHuEPO) and darbepoetin in MDS patients [133–135]. The first meta-analysis (59 studies, 1936 patients) analysed controlled and single-arm studies separately [135]. In controlled trials, including mainly patients with low to intermediate-1 International Prognostic Scoring System (IPSS) risk who have been randomised to rHuEPO with or without granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), an Hb response was reported for 27.3% of ESA-treated patients compared with 6.7% in the control groups ($P < 0.01$). In single-arm studies, pooled response rates were 32.1% for rHuEPO and 48.1% for darbepoetin alpha. Patient groups with lower endogenous EPO levels at baseline, longer treatment periods or iron supplementation showed higher Hb response rates. A second meta-analysis (30 studies, 1314 patients) that included more recent trials with higher ESAs dosing reported overall response rates of 57.6% (rHuEPO) and 59.4% (darbepoetin alpha) [133]. Three factors predicted response to rHuEPO: baseline serum EPO < 500 IU/L, French–British–American (FAB) class [either refractory anaemia (RA) or RA with excess blasts (RARS)] and fixed rather than weight-adjusted dosages. Neither of these two meta-analyses showed an increased risk of haematological or cardiovascular events or leukaemic transformation in patients receiving ESAs. No direct comparison between the different ESAs could be made. The third meta-analysis (15 studies, 741 patients) indicated equivalent erythroid response in patients treated with rHuEPO alpha alone (standard dose 30 000–40 000 IU weekly) or in combination with G-CSF or GM-CSF [134]. High-dose rHuEPO alpha monotherapy (60 000–80 000 IU weekly) resulted in significantly higher response rates compared with standard-dose treatment (64.5% versus 49.0%). Achievement of higher response rates with higher EPO doses was independent of FAB subtype or classification and transfusion dependency. So far, there is no evidence for a negative impact on survival or acute myeloid leukaemia (AML) evolution in prospective or historical controls [136–138]; however, in patients that progressed to AML, ESAs should not be used. Prospective randomised studies showed no OS benefit of ESA treatment in patients with MDS. In contrast to patients with solid tumours, there seems to be no association between the use of ESAs and thrombosis in patients with MDS [139], although this may also be related to the fact that patients with MDS only rarely receive(d) ESAs to achieve Hb levels > 12 g/dL.

Biosimilars and follow-on products

rHuEPO and recombinant G-CSF were the first biotechnological medicinal products used in haematology. More recently, follow-on products (biosimilars) of epoetin have been granted marketing authorisation by the EMA [140, 141]. A biosimilar is a biological medicinal product (a medicine produced by or derived from a biological source) that is similar to another biological medicinal product that has already been authorised for use in Europe [142]. Biological medicinal products similar to a reference medicinal product do not usually meet all the conditions to be considered as a generic medicinal product, mainly due to manufacturing process characteristics, raw materials used and molecular characteristics. Authorisation of a biosimilar requires studies showing that the product is similar to the reference medicine and does not have any meaningful differences from the reference medicine in terms of quality, safety or efficacy, yet the amount of information on safety and efficacy required is usually less than the amount required to authorise an original biological medicinal product [143].

Notably, only products that are approved, produced and distributed according to a strict biosimilar guidance of a regulatory authority such as the EMA or the Food and Drug Administration (FDA) should be considered as biosimilar and be differentiated from products that are not manufactured and quality-controlled in compliance with the biosimilar guidance or even counterfeit medicines. Use of epoetin products that have not been approved by the EMA has been linked to an increased incidence of antibody-mediated pure red cell aplasia (PRCA). Among 30 patients with renal insufficiency who experienced a sudden loss of response after the switch from an epoetin originator, 23 were positive for antibodies to rHuEPO and all of them had PRCA, compared with none in the seven antibody-negative patients [144]. Whether this increased rate of antibody-mediated PRCA cases is actually related to quality-controlled non-originator products or an increased background of idiopathic PRCA in the population [145] or an elevated content of protein aggregates in counterfeit or smuggled products with interrupted cold chain (2–8 °C) [146] cannot be clarified.

Head-to-head trials and long-term follow-up with biosimilars of epoetin that were manufactured and distributed according to established and regularly updated biosimilar guidelines like the scientific guidelines on biosimilar medicines issued by EMA have shown the safety and therapeutic equivalence of biosimilars and originator products in patients with renal insufficiency [147–150] and oncology patients [151]. The effectiveness of a biosimilar epoetin has also been shown for patients with CIA in clinical practice [152].

Independently of which epoetin has been used to initiate treatment, switching preparations in responsive and stable patients should be avoided [153] to prevent issues of immunogenicity and confused pharmacovigilance reports [V, C]. Automatic substitution should be only allowed in drug-naïve patients and if the clinician accepts a therapeutic equivalence [153]. Furthermore, reliable monitoring of treatment outcomes with biosimilars is crucial to substantially increase the numbers of recorded patient-years under treatment above those requested for regulatory approval; another reason why the use of different preparations within one patient should be avoided.

Regulatory evaluation of i.v. iron follow-on products is currently determined by the pathway for generic medicinal products. However, there is growing clinical [154–157] and non-clinical [158] evidence raising doubts about the interchangeability and/or substitutability of these complex drugs [159]. Concerns regarding the regulatory assessment of nanoparticle iron follow-on products are also highlighted by the EMA in a reflection paper on non-clinical and clinical data requirements [160]. Accordingly, new regulatory approaches that focus more on comparability of clinical safety and therapeutic efficacy are required (and are emerging) for the approval of follow-on products of such non-biological complex drugs [161, 162]. As for biosimilars, switching preparations in adequately treated patients and automatic substitution should be avoided [V, C].

Conclusions

The largest amount of evidence in the treatment of symptomatic CIA is available for ESAs. ESAs are relatively safe except for an increased risk of VTE and development of PRCA in very rare cases. Outside approved indications, ESAs have been linked with increased mortality.

i.v. iron has been shown to significantly enhance the activity of ESAs, but long-term results are not available. As a sole therapy, i.v. iron improves anaemia in cancer patients with ID, but representative, randomised studies and long-term data are lacking.

Opposite the large number of ESA studies in cancer patients, no randomised trials have investigated the use of RBC transfusions in this population. Based on findings from studies in non-oncology populations and cancer patients undergoing surgery, it is recommended that RBC transfusions are reserved for patients with Hb levels below 7–8 g/dL and situations when rapid improvement of severely symptomatic anaemia is required [II, B].

MDS patients with low to intermediate-1 risk (IPSS) or very low to intermediate risk (revised; IPSS-R) disease and symptomatic anaemia should be considered for ESA therapy, despite the fact that not all ESAs are currently EMA-approved for use in patients with MDS [I, A].

The FDA recently determined that the ESA Risk Evaluation and Mitigation Strategy (related to the use of ESAs to treat patients with anaemia due to associated myelosuppressive chemotherapy) was no longer necessary to ensure that the benefits outweigh the risks of shortened OS and/or increased risk of tumour progression or recurrence in patients with cancer [163]. In addition, the FDA's Oncology Drugs Advisory Committee has recently recommended approval of a biosimilar to epoetin alpha [164].

In Europe, recently published German guidelines have reached similar conclusions about the adequate safety and appropriate use of ESAs [165].

Personalised medicine

Although these guidelines take into account the Hb, vitamin and iron levels of patients before treatment is applied, personalised medicine requires an individualised approach. Further research is needed on potential markers to determine the best chances of

Table 5. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [23].

response to the applied agents, in particular to iron and epoetins. Ongoing studies on hepcidin might provide an insight for better use of i.v. iron.

Follow-up, long-term implications and survivorship

Long-term data on both the safety and OS data of i.v. iron in the setting of cancer patients are not currently available. Other issues are described and discussed in the above text.

Methodology

Since the last European anaemia treatment guidelines were published (ESMO in 2010, EORTC in 2007), new data about treatment options for cancer-related anaemia and CIA have become available. In addition, treatment options for anaemia in patients with MDS of IPSS and/or IPSS-R lower risk have been evaluated. The authors conducted electronic searches of the Medline database for English language records from 2007 to March 2015 (search terms: cancer, tumour, haematological malignancy, MDS, chemotherapy, anaemia, erythropoiesis, iron, vitamin, folate, deficiency and combinations thereof) and manually searched abstract books of the major international oncology congresses. The authors met in March 2013, 2014 and 2015 to discuss the findings and agreed on a consensus for the guidelines in several meetings and phone conferences and reviewed the manuscript during 2016–2017. These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology).
The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Table 5. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

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