Gloucestershire Hospitals
NHS Foundation Trust

Investigation and Management of Anaemia and Iron Deficiency in Oncology Patients

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1. Introduction

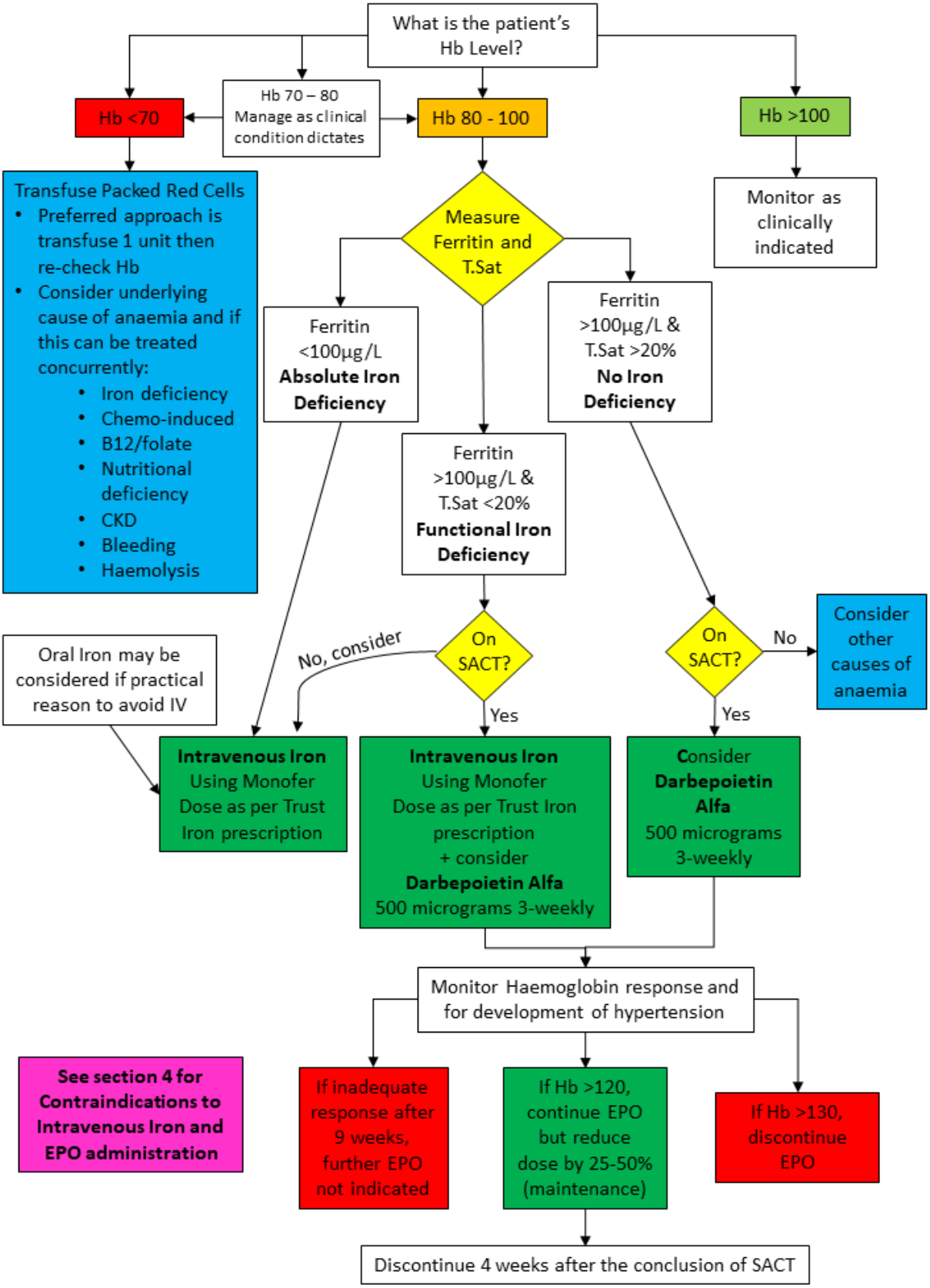
Anaemia is a common finding in Oncology patients, both in patients on and off systemic anti-cancer therapy (SACT). There are many potential causes of anaemia in these patients, including:

- Iron deficiency
- Vitamin deficiency eg B12, folate
- Blood loss, either acute or chronic, including iatrogenic due to regular blood tests
- Chronic inflammation or 'Anaemia of chronic disease'
- Bone marrow infiltration by malignant cells
- Bone marrow suppression as a result of SACT or Radiotherapy
- Chronic Kidney Disease
- Malnutrition/cachexia
- Haemolysis

Anaemia and iron deficiency are negative prognostic factors in multiple types of cancer (1, 2) and correlate with poor performance status. Anaemia is a contributing factor to fatigue which is an important symptom affecting quality of life in Oncology patients.
Anaemia in Oncology patients has often historically been treated with Red Cell transfusion when the patient reaches a clinical threshold of a Haemoglobin level of <70-80 g/L or has significant symptoms of anaemia. Repeated blood transfusion is associated with increased risk of adverse transfusion reactions. There is also a pressing need to spare blood resources at a national level.

2. Aim

The aim of this guideline is to assist in the investigative work-up and management of patients with anaemia in the context of a diagnosis of a solid tumour malignancy. The objective is to improve recognition of clinically significant anaemia and iron deficiency and inform proactive treatment decisions, intervening earlier in the patient's development of anaemia with non-blood product interventions. This should enable judicious use of blood products, in accordance with the Trust's Transfusion Policy (3).



Trust Monofer Prescribing Chart:
https://www.gloshospitals.nhs.uk/media/documents/SAMPLE_Ferinject_Monofer_drug_chart_jVv1oZU.pdf

3. Diagnosis

In a general clinical context, anaemia is defined as a Haemoglobin value of ≤130 g/L for male patients and ≤110 g/L for female patients.
For the purposes of this guideline, a threshold of **≤100 g/L will be used to define clinically significant anaemia** that should be investigated and treated, particularly in the context of ongoing or planned oncological treatment.

The European Society for Medical Oncology (ESMO) Guidelines (4) recommend that **Ferritin and Transferrin Saturation (T.sat) values** are measured in Oncology patients with anaemia to ensure that iron deficiency is diagnosed and can be treated effectively. Ferritin is measured by the Haematology laboratory (Purple or Gold blood sample tube required). Transferrin saturation is calculated from the serum Iron and Transferrin values, assayed by the Biochemistry laboratory (Gold or Rust blood sample tube required).
B12 and folate levels should also be measured, as these may be corrected easily if deficient. Do not rely on Mean Cell Volume (MCV) being in the normal range for diagnosing iron deficiency.

Iron deficiency may be sub-divided into two categories:

- Absolute Iron Deficiency – where there is a true total body iron deficit, defined in this patient group as a serum Ferritin value of <100 µg/L (sometimes expressed in ng/ml)
- Functional Iron Deficiency – where total body iron stores may not be depleted, but iron is not bioavailable for Haemoglobin synthesis. This is defined by a Transferrin Saturation value of <20% (and may be associated with a Ferritin value >100 µg/L)

Other causes of anaemia, as outlined in the Introduction, should be considered based on the patient's history and examination.

4. Treatment

Recommendations for treatment of Iron Deficiency and Anaemia are adapted from the European Society for Medical Oncology (ESMO) Guideline, October 2018 (5). Treatment should be with the intention of maintaining haemoglobin at a level above that at which blood product transfusion would be required.

When Haemoglobin level is 70 – 80 g/L, the management strategy will depend on the burden of the patient's symptoms and co-morbidities, such as ischaemic heart disease and heart failure.

A Haemoglobin response to Intravenous Iron is expected to take a minimum of 2-4 weeks and this should be accounted for when assessing patients and planning treatment, bearing in mind the rate of decrease in Haemoglobin or worsening of anaemia-related symptoms.

Iron Deficiency

There is evidence that oral iron is much more likely to be ineffective, or add to the burden of drug-related side effects that patients experience and is therefore not recommended for routine use in Oncology patients. Intravenous iron therapy is preferred.
The preparation of choice in Oncology is **Monofer**, which can be administered in a single session over 15-30 minutes. It should be prescribed using the Trust prescription chart (6), accessed at:
https://www.gloshospitals.nhs.uk/media/documents/SAMPLE_Ferinject_Monofer_drug_chart_jVv1oZU.pdf

Patients who are Iron deficient and being considered for Erythropoiesis-Stimulating Agents should receive Iron replacement prior to initiation of ESA therapy, to maximise the chance of an effective response to treatment.

Contraindications to Intravenous Iron administration

- Hypersensitivity to Intravenous Iron preparations
- Iron overload
- Inadequately controlled infection
- Decompensated liver disease

Chemotherapy-induced anaemia and use of Erythropoiesis-Stimulating Agents (ESAs or EPO)

For patients in whom it is believed that myelosuppression from SACT is a cause of their anaemia, Darbepoetin is licensed for use by NICE in Technology Appraisal 323 (7). Darbepoetin can be prescribed on Chemocare as part of the patient's regular SACT prescription. It can be administered as a subcutaneous injection during the patient's regular SACT appointment. Trust policy recommends dosing 3-weekly at a flat initial dose of 500 micrograms. Alternatively, once-weekly dosing can be given at 2.25 micrograms/kg of body weight (8).

Patients should have Ferritin and Transferrin saturation levels checked prior to commencing Darbepoetin, as patients with inadequate Iron reserves may fail to respond adequately to Darbepoetin. Patients with normal Iron studies prior to ESA treatment may be rendered functionally Iron deficient during ESA treatment, due to use of Iron reserves in Haemoglobin synthesis. **For patients who are iron deficient during SACT, consider treating with iron and assessing for haemoglobin response prior to starting EPO, as Hb may improve with Iron alone.**

The response to Darbepoetin treatment should then be monitored at the interval recommended for the patient's ongoing SACT. If the clinical response of the patient (fatigue, haemoglobin response) is inadequate after nine weeks, further therapy is unlikely to be effective and it should therefore be discontinued.

If responding to ESA treatment, once the target Haemoglobin level for the patient has been reached, the Darbepoetin dose should be reduced by 25-50% and continued as maintenance treatment. Appropriate dose titration between 500 micrograms, 300 micrograms and 150 micrograms should be considered. If the Haemoglobin level ≥ 120 g/L, the dose should be further reduced by 25-50%.

Patients should be monitored for hypertension during ESA therapy, with hypertension managed as per usual standards.

EPO therapy should be discontinued 4 weeks after the conclusion of SACT, or withheld if the Haemoglobin level ≥ 130 g/L. Patients should be monitored for development of hypertension during initiation and maintenance with Darbepoetin.

Contraindications to ESA treatment

- Hypersensitivity to darbepoetin, sodium phosphate monobasic, Sodium phosphate dibasic, Sodium chloride or polysorbate 80
- Poorly controlled hypertension
- Radical intent treatment
- Patient not receiving Systemic Anti-Cancer Treatment
- High VTE risk

Blood Transfusion

In the case that the patient's Haemoglobin level is < 70g/L (or < 80 g/L in the context of significant cardiac comorbidity), blood transfusion should be considered, if appropriate in the context of the patient's disease state. Where possible, consider transfusing 1 unit of Red Cells and re-evaluating Haemoglobin response.

Monitoring of Iron Studies during ongoing treatment

Ferritin and Transferrin saturations should not usually be re-evaluated more often than every 3 months, as this will affect overall testing capacity and is unlikely to yield further clinical information. It may be considered if inadequate clinical response to Iron or ESA treatment is achieved. If adequate Haemoglobin response is achieved, Iron studies do not need to be routinely reassessed.

References

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4. Aapro M, Beguin Y, Bokemeyer C, Dicato M, Gascón P, Glaspy J, Hofmann A, Link H, Littlewood T, Ludwig H, Österborg A, Pronzato P, Santini V, Schrijvers D, Stauder R, Jordan K, Herrstedt J; ESMO Guidelines Committee. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv96-iv110. doi: 10.1093/annonc/mdx758. Erratum in: Ann Oncol. 2018 Oct 1;29(Suppl 4):iv271. PMID: 29471514.
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