

Anaemia and cancer: oral or intravenous iron?

Anaemia and absolute or functional iron deficiency (ID) are common issues among cancer patients, with the prevalence of ID ranging from 32% to 60%. Most randomised clinical trials have shown superior efficacy of IV iron over oral or no iron supplementation in anaemic cancer patients receiving erythropoiesis-stimulating agents. Intravenous iron supplementation reduced blood transfusions, increased haemoglobin, and improved quality of life. At recommended doses, IV iron is well tolerated, and allergic reactions are exceedingly rare with modern formulations. Oral iron is often poorly tolerated and this can lead to compliance issues.

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Cancer patients, especially those

receiving chemotherapy, frequently suffer from anaemia and iron deficiency (ID).^{1,2} Reports on the prevalence of ID are still scarce but estimates range from 29% to 60%, depending on the tumour type and patient population.¹ Nevertheless, the role of ID seems to be underestimated, although data in cancer patients suggest a significant correlation between ID and worse World Health Organization (WHO) performance scores.³ Even in non-anaemic healthy individuals, ID can be associated with impaired physical function and fatigue that respond to iron therapy.¹ The importance of iron in anaemia management is increasingly recognised and anaemia treatment guidelines

recommend minimising the use of erythropoiesis-stimulating agents (ESAs) and blood transfusions because of the associated risks.⁴⁻⁶

Pathophysiology and diagnosis

Chronic blood loss and nutritional deficiencies can aggravate anaemia in cancer patients; however, anaemia of chronic disease (ACD) and chemotherapy-induced anaemia (CIA) are the major causes. Chronic diseases, including cancer, are associated with proinflammatory cytokine patterns, which, in turn, upregulate hepcidin, the key regulator of iron homeostasis. As a consequence of high hepcidin levels, iron cannot be mobilised sufficiently from physiological iron stores in cancer patients,⁷ especially in patients treated with an ESA who have an

deficiency), whereas insufficient availability of iron is indicated by low transferrin saturation (TSAT <20%) even if serum ferritin levels are normal or elevated (often referred to as functional iron deficiency; FID).¹ Other markers of iron-restricted erythropoiesis are not recommended in daily practice.

Treatment of ID and anaemia

Treatment options for anaemia in cancer patients include blood transfusions, ESAs and iron supplementation. However, a main goal of anaemia treatment guidelines is reducing the reliance on blood transfusions.⁴⁻⁶ Transfusions still bear risks such as transfusion reactions and transmission of known and unknown infectious diseases, and may increase the risk of cancer recurrence, mortality, stroke

“Treatment options for anaemia in cancer patients include blood transfusions, ESAs and iron supplementation”

elevated demand for iron due to rapidly increased red blood cell production. Because hepcidin also affects the release of iron from enterocytes, the absorption of nutritional iron and oral iron preparations is also impaired, thereby further increasing the risk of ID and anaemia. Routine diagnosis of ID has to identify both insufficient iron stores for successful ESA therapy and insufficient availability of iron for effective erythropoiesis. Depleted iron stores are indicated by serum ferritin levels <100ng/ml (absolute iron

and myocardial infarction).^{1,8}

One option to reduce transfusion requirements of cancer patients is the addition of ESAs to therapy, yet the European Medicines Agency (EMA) highlighted that ESA use should be restricted for cancer patients with clearly symptomatic anaemia who receive chemotherapy.¹ Furthermore, initiation of ESAs is limited to patients with haemoglobin (Hb) <10g/dl and dose reductions are required if Hb increase is ≥1g/dl within two weeks. Limits in

response rate (30–75%, probably due to absolute or functional ID), can be overcome with IV iron, as acknowledged by anaemia treatment guidelines in oncology.^{4–6} Intravenous iron should be particularly considered in patients with FID (that is, ferritin levels up to 800ng/ml if TSAT is <20%). Active infection is considered as the only restriction to iron supplementation.¹

The efficacy of IV iron supplementation in cancer patients treated with ESAs for chemotherapy- or cancer-related anaemia has been shown in six randomised, controlled clinical trials.¹ Notably, studies in patients who were not iron-deficient at enrolment achieved a 13–19% absolute increase in response rate, confirming that high IV iron doses can overcome hepcidin-mediated reduction of iron release from the reticuloendothelial system. Only one study using an unusual (off-label) dosing schedule did not show a significant benefit of IV iron supplementation.⁹

An oral iron arm was included in three of these studies^{9–11} and did not show a significant benefit of oral iron compared with no iron supplementation. Conversely, IV iron, given at recommended doses, significantly improved haematologic response compared with oral and no iron supplementation.^{10,11} Therefore, oral iron might only be considered in patients with absolute ID and adequate tolerance of oral iron but no impairment of iron resorption

“Intravenous iron may be effective in the reduction of ESA doses and blood transfusions in cancer patients with anaemia”

and no, or only minor, symptoms. ESA-treated patients (receiving concomitant chemotherapy) who have ID should receive IV iron therapy.⁵ Meta-analyses of publications and abstracts on trials comparing IV iron with no or oral iron supplementation of ESA therapy (including the seven studies discussed above) showed a significantly increased chance (29–31%) to achieve a haematopoietic response with IV iron supplementation, and a 23% reduction in the risk of transfusion.¹

Dosing of IV iron

Most studies on IV iron supplementation used a total dose of approximately 1000mg iron.¹ One study compared multiple administrations of 100mg iron with a total dose infusion of 1000–3000mg and found no difference in haematologic response.¹²

Table 1: Approved IV iron preparations

INN	Brand name (originator)
Ferric carboxymaltose	Ferinject
Iron dextran	Cosmofer
Iron isomaltoside	Monofer
Iron sucrose	Venofer
Sodium ferric gluconate	Ferlecit
Ferumoxylol*	Rienso*

INN, International Non-proprietary Name of active substance

* Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation

Intended copies of originator IV iron compounds have been approved via the generic pathway in different countries. Because subtle differences in the manufacturing process can affect the physicochemical and biological properties of these compounds, clinical head-to-head comparisons between the copies and the reference product are recommended for confirmation of therapeutic and toxicologic equivalence.¹

Therefore, we recommend a single dose of 1000mg iron (if feasible with the available IV iron formulations; Table 1) in patients with functional iron deficiency. If no haemoglobin response is observed six weeks after initial treatment, iron status parameters should be checked. In patients with absolute iron deficiency, we recommend following the product label.

Sole or supplemental treatment with IV iron?

In anaemic cancer patients with ID, guidelines recommend treatment of ID before initiation of an ESA. Because impaired iron utilisation is a main cause of anaemia, iron treatment alone may already

serve as anaemia treatment. In non-cancer populations with chronic disease (inflammatory bowel disease, chronic heart failure), IV iron as sole anaemia treatment could resolve anaemia. In cancer patients, however, studies examining IV iron as sole anaemia treatment are only just starting to emerge. Two small studies in patients with gynaecologic cancers showed promising results, and a recent report suggests that IV iron supplementation without addition of an ESA might improve Hb levels in patients with cancer.¹³

Economic aspects of IV iron in anaemia therapy

Anaemia significantly increases annual healthcare costs (\$34,009 versus \$9,034 for anaemic versus non-anaemic cancer patients; $p < 0.001$)¹⁴ and ESAs are a major

cost factor. Treatment supplementation with IV iron can reduce ESA dose (and transfusion) requirements and thereby result in substantial cost savings in the treatment of cancer-related anaemia.^{1,15} Among the different IV iron preparations, the number and duration of required infusions mainly influence the treatment costs.¹⁶

Safety of IV iron in clinical routine

The tolerability of IV iron in ESA-treated patients has been confirmed in six randomised, controlled clinical trials. No differences in adverse event rates were observed between IV iron and control treatment arms.¹ One trial that reported higher adverse event rates in the IV iron arm used high individual doses of sodium ferric gluconate that exceeded the recommended dose by 50% (187.5 compared with 125 mg iron per administration).¹⁹ Intravenous iron infusions can be associated with adverse infusion reactions. In routine practice, allergic and anaphylactoid reactions are rare and mainly associated with iron dextrans. A recent study that analysed adverse events reports separately for Europe and North America showed a higher rate of anaphylactic reactions also for low molecular weight iron dextrans (15.6 events per million 100mg iron dose equivalents) compared with iron sucrose and ferric gluconate (0.9 and 0.4 events per million 100mg iron dose equivalents, respectively).¹⁷

Oral iron is well known for its gastrointestinal intolerance, which also affects patients' adherence with therapy.¹ Among studies investigating oral and IV iron in ESA-treated anaemic cancer patients, Henry et al¹¹ reported drug-related adverse events in 31.1% of patients

in the oral iron arm compared with 12.7% in the IV iron arm (no details on statistical significance of the difference were reported).

Limitations to the use of IV iron in clinical practice

Although not specifically investigated in human studies, potential interactions of iron with cells of the immune system and certain chemotherapies (for example, anthracyclines and platinum-based therapies) may be considered as limits to IV iron use until availability of human data.¹⁷ In clinical trials, no increased rate of infections was observed in IV iron-treated cancer patients but animal studies suggest that IV iron administration should be avoided during active sepsis. In patients receiving cardiotoxic chemotherapy, concomitant administration of IV iron and cytotoxic drug therapy may be avoided, and IV iron given either before administration of chemotherapy or at the end of a treatment cycle; just before the next cycle.¹

Some epidemiological studies showed that conditions with long-term iron overload are associated with the induction of new cancers. This gave rise to uncertainty on the potential role of iron in tumour progression. A recent clinical review has not identified any related clinical concern but long-term follow-up data in cancer patients are not yet available.¹

Conclusions

Intravenous iron improved response rates to anaemia treatment in published randomised, controlled trials, whereas no significant benefit of oral iron has been seen in the investigated ESA-treated cancer patient populations. Furthermore, IV iron may be effective in the reduction of ESA doses and blood transfusions. Results of a few studies that investigated the use of IV iron as first-line anaemia therapy suggest that IV iron as sole anaemia therapy can benefit some patients, and addition of an ESA may be considered for patients not responding to IV iron alone. Nevertheless, confirmation of long-term safety requires larger randomised, controlled studies with long-term follow-up. ●

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Key points

- Iron deficiency (ID), especially functional iron deficiency, is a frequent comorbidity across different tumour types. ID is a main cause of anaemia and associated with worse performance status.
- Iron status should be assessed at initial diagnosis, and during any kind of anti-anaemia therapy to warrant timely commencement of iron supplementation.
- In cancer patients, transferrin saturation <20% indicates insufficient availability of iron despite normal or elevated serum ferritin levels (functional iron deficiency). Serum ferritin <100ng/ml probably indicates depleted iron stores (absolute iron deficiency).
- IV iron supplementation of ESA therapy significantly increased haematopoietic response and reduced the risk of blood transfusion. Growing evidence suggests that IV iron supplementation without addition of an ESA might improve haemoglobin levels in patients with cancer.
- In cancer patients, a single dose of 1000mg iron (if possible) is recommended for the treatment of functional iron deficiency. At recommended doses, IV iron is well tolerated; no increase in infections or new adverse events were observed in clinical trials.

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