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Prevalence and management of cancer-related anaemia, iron deficiency and the specific role of i.v. iron

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Background: Chronic diseases reduce the availability of iron for effective erythropoiesis. This review summarises clinical consequences of iron deficiency (ID) and anaemia in cancer patients, mechanisms how impaired iron homeostasis affects diagnosis and treatment of ID, and data from clinical trials evaluating i.v. iron with or without concomitant erythropoiesis-stimulating agents (ESAs).
Design: Clinical trial reports were identified in PubMed and abstracts at relevant major congresses.
Results: Reported prevalence of ID in cancer patients ranges from 32 to 60% and most iron-deficient patients are also anaemic. Randomised clinical trials have shown superior efficacy of i.v. iron over oral or no iron in reducing blood transfusions, increasing haemoglobin, and improving quality of life in ESA-treated anaemic cancer patients. Furthermore, i.v. iron without additional ESA should be evaluated as potential treatment in patients with chemotherapy-induced anaemia. At recommended doses, i.v. iron is well tolerated, particularly compared with oral iron. No serious drug-related adverse effects were seen during long-term use in renal disease and no effect on tumour growth has been observed in trials with anaemic cancer patients.
Conclusions: Reliable diagnosis and treatment of ID are recommended key steps in modern cancer patient management to minimise impact on quality of life and performance status.
Key words: anaemia, chemotherapy-induced anaemia, diagnosis, intravenous iron, iron deficiency, hepcidin

introduction

Iron deficiency (ID) and anaemia are frequent complications in cancer patients, in particular during treatment with chemotherapeutic agents [1–3]. ID, even in the absence of anaemia, may be associated with impaired physical function, weakness, and fatigue that can be ameliorated by iron therapy [4]. If left untreated, ID can lead to anaemia; thus, the potential effect of ID on vulnerable populations such as cancer patients should not be underestimated.

Current guidelines on the treatment of cancer-related anaemia recommend restricted usage of erythropoiesis-stimulating agents (ESAs) and reduction/prevention of blood transfusions [5–8]. Data from several controlled clinical trials have shown that i.v. iron supplementation enhances response to ESA treatment and can reduce administered ESA doses in cancer patients [9–14]. Early results from clinical trials on i.v. iron treatment without concomitant ESAs suggest that initiation of anaemia treatment with i.v. iron alone should be investigated as treatment option for cancer-related anaemia [15, 16].

This review focuses on the clinical consequences of ID and anaemia in cancer patients along with data from clinical trials using i.v. iron highlighting the evolving role of i.v. iron therapy in cancer patient management. In addition, mechanisms behind cancer-related anaemia that influence the correct diagnosis and treatment of ID or the maintenance of iron availability are discussed.

search strategy and selection criteria

Data from appropriate clinical trials were identified by screening the US National Library of Medicine's PubMed database with the search terms 'cancer', 'intravenous iron' or 'parenteral iron', and 'anaemia', and limiting the search to clinical trials reported in English. Data reported in abstract form only were identified by manual search through abstracts at major congresses in the field.

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prevalence and burden of ID and anaemia in cancer patients

The high prevalence of anaemia in patients with different cancer types (39% at enrolment and 68% becoming anaemic at least once during the 6-month survey period) has been already shown in the European Cancer Anaemia Survey (ECAS) [1]. Conversely, published data on the prevalence of ID in cancer patients are scarce (Table 1) [2, 3, 17–19]. Reported prevalence of ID was highest for colorectal cancer (60%, and 69% of those were also anaemic) [2]; probably, chronic blood loss may render patients with colorectal or gastrointestinal cancers more prone to ID and anaemia. Nevertheless, also in other populations, the prevalence of ID and anaemia was considerably high (29%–46% and 7%–42%, respectively) [3, 17–19].

Currently, data on the impact of ID in cancer patients are only available in abstract form, suggesting a significant correlation between low iron status and worse World Health Organisation (WHO) performance scores [19]. Correction of ID in a noncancer population (patients with chronic heart failure) significantly improved exercise capacity, quality of life, and disease state independently whether patients were anaemic or not [20].

More data are available on the impact of anaemia, showing a 65% increased risk of death [21] and close to fourfold higher average annual health care cost per patient [22]. A causal relation between anaemia and the risk of death remains to be confirmed before the final conclusion that correcting anaemia improves prognosis. Two large analyses demonstrated the relationship between haemoglobin (Hb) levels and physical performance as well as quality of life in cancer patients [1, 23]. In ECAS, patients with the poorest WHO performance scores (2–4) were more likely to have low Hb levels ($P < 0.001$). A direct correlation between quality of life and Hb levels in cancer patients receiving chemotherapy has been shown across the clinically relevant Hb range of 8–14 g/dl. Accordingly, Hb increase achieved with i.v. iron supplementation of ESA treatment in patients with chemotherapy-related iron deficiency anaemia (IDA) was associated with significantly better effects on energy level, activity, and overall quality of life ($P < 0.0002$) [9].

causes and diagnosis of ID and anaemia

impaired iron utilisation in chronic disease

Anaemia of chronic disease (ACD) and chemotherapy-induced anaemia (CIA) are the major causes of anaemia in cancer patients and can be aggravated by chronic blood loss and nutritional deficiencies (e.g. due to cancer-induced anorexia or resection of gastrointestinal malignancies). In patients with ACD, the availability of iron is affected by hepcidin, the key regulator of iron homeostasis (Figure 1) [24, 25]. Increased hepcidin levels block the ferroportin-mediated release of iron from enterocytes and macrophages [25]. In the long term, this can lead to absolute ID (AID, insufficient iron stores) due to impaired utilisation of nutritional or orally administered iron. In the short term, this 'hepcidin block' can result in functional iron deficiency (FID), a condition under which iron cannot be efficiently mobilised from stores in the reticuloendothelial system (RES) [24]. In patients with inflammation, iron release is reduced to 44% compared with normal subjects (Figure 2) [26]. Thus, even iron-replete patients can experience a shortage of available iron, especially when exposure to ESAs rapidly increases red blood cell production [28].

Inflammatory cytokines also inhibit proliferation and differentiation of erythroid progenitor cells and blunt endogenous erythropoietin production in the kidney [29]. In addition, reduced sensitivity to erythropoietin, a reduced life span of erythrocytes, solid tumours or metastases infiltrating the bone marrow, and myelosuppressive effects of chemotherapies can impair normal haematopoiesis [25, 30–32].

diagnostic markers of ID in patients with chronic disease

Serum ferritin, the most commonly assessed marker, generally reflects the status of iron stores while transferrin saturation (TSAT), the percentage of hypochromic red cells (%HYPO), and the Hb content of reticulocytes (CHr) better reflect the availability of iron [33]. Since serum ferritin, an acute-phase protein, can be elevated due to inflammation and liver cell damage, normal or elevated ferritin levels do not necessarily indicate sufficient iron stores, particularly in cancer patients

Table 1. Reported prevalence of iron deficiency in different cancer patient populations

	Tumours/Patients (*N*)	% with ID	Definition of ID	% with IDA
Kuvibidila, 2004 [3]	Prostate (34)	35	SF < 12 ng/ml[a]	n/a
		32	TSAT < 16%	
Beale, 2005 [2]	Colorectal (130)	60	SF < 15 ng/ml and/or TSAT < 14%	42[b]
Steinmetz, 2010 [17]	CIA (286)	29	FI > 3.2[c] or CHr ≤ 28 pg	7[d]
Beguin, 2009 [18]	CIA (481)	43	SF < 100 ng/ml and/or TSAT < 20%	n/a
Ludwig, 2011 [19]	Solid tumours (1053)	46	SF < 30 ng/ml or TSAT < 20%	33

[a]Or <100 ng/ml in subjects with inflammation.
[b]Hb < 12.5 g/dl in men and Hb < 11.5 g/dl in women.
[c]Morr than 2.0 in subjects with C-reactive protein levels >5 mg/l.
[d]FI ≤ 3.2 (or 2.0) and CHr ≤ 28 pg.
ACD, anaemia of chronic disease; CHr, haemoglobin content of reticulocytes; CIA, chemotherapy-induced anaemia; FI, ferritin index (soluble transferrin receptor/log ferritin); FID, functional iron deficiency; ID, iron deficiency; IDA, iron deficiency anaemia; SF, serum ferritin; TSAT, transferrin saturation.

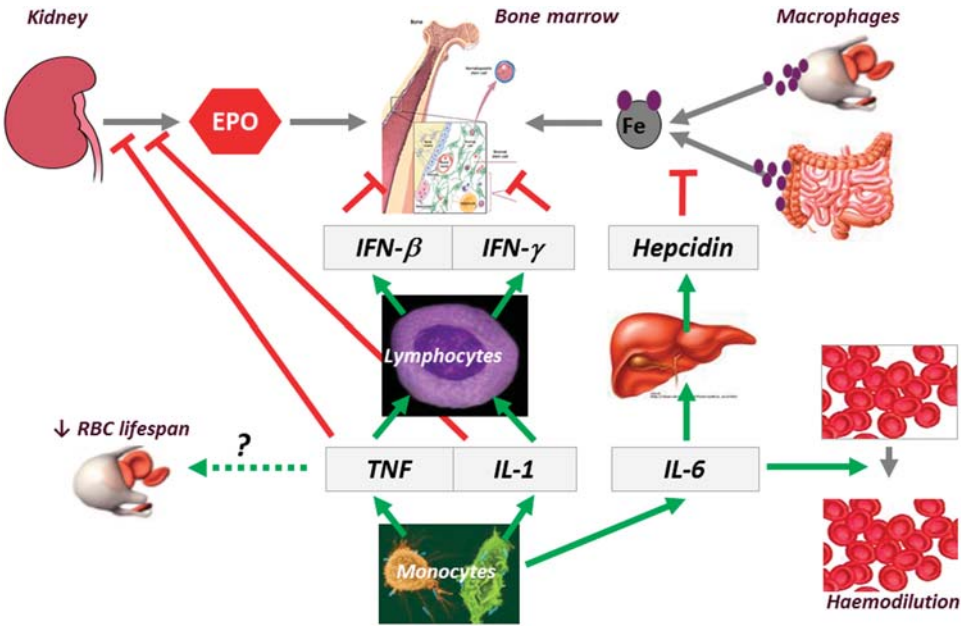

Figure 1. Hepcidin-mediated blockade of iron homeostasis due to inflammation in anaemia of chronic disease. During inflammation, monocytes release cytokines such as tumour necrosis factor (TNF), interleukin (IL)-1, and IL-6. Red blood cell (RBC) lifespan is reduced possibly through a TNF-dependent mechanism. TNF and IL-1 impair erythropoietin (EPO) production by the kidney and induce lymphocytes to release interferons that in turn inhibit the proliferation and differentiation of erythroid progenitor cells. On the other hand, IL-6 worsens anaemia through expansion of plasma volume. IL-6 also increases hepcidin secretion by the liver, thereby inhibiting iron absorption and iron release from macrophages [24].

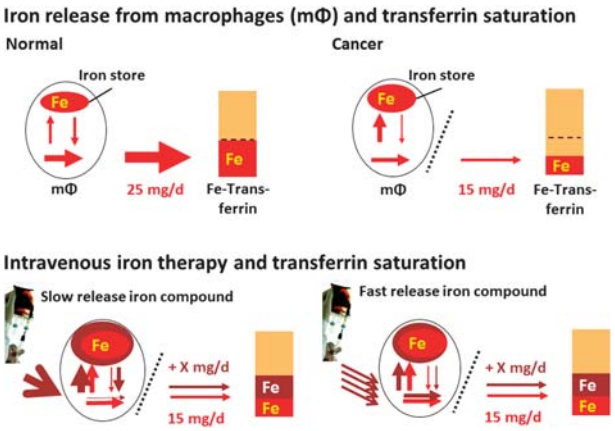

Figure 2. Intravenous iron overcoming the iron blockade in patients with chronic disease. Intravenous iron can overcome the iron blockade in patients with chronic disease and elevated hepcidin levels. Iron entering macrophages as senescent RBC (in red) or i.v. iron (in brown) can either be released immediately (and saturate plasma transferrin to a certain degree) or be stored in ferritin. Compared with the 25 mg daily iron release from macrophages in normal individuals, this rate decreases to ~15 mg/day in patients with inflammation [26]. In such patients, stable i.v. iron–carbohydrate complexes release the iron over a prolonged period of time, so that large iron doses can be injected once, while iron from less stable complexes is released rapidly by macrophages and therefore requires multiple low-dose injections [27].

[34]. Thus, routine blood analysis should also include C-reactive protein (CRP) and alanine aminotransferase (ALT) to check for inflammation and liver function. Soluble transferrin receptor levels, recently suggested for allocation of cancer patients to treatment with ESA alone, iron alone or a combination thereof [17, 35], rather reflect the erythropoietic activity than the iron status and cannot be used as iron status parameter when erythropoiesis is stimulated, e.g. with ESAs. Therefore, in routine clinical practice, serum ferritin levels <100 ng/ml probably indicate insufficient iron stores for successful ESA therapy in patients with cancer, and the combination of low TSAT (<20%) and normal or even elevated serum ferritin may indicate FID (Figure 3) [34].

The potential of TSAT as marker of FID has been shown in patients with lymphoproliferative malignancies, where 39% of patients presented with a TSAT <20% despite detectable iron deposits in the bone marrow [12]. During the subsequent clinical study, mean levels dropped in patients receiving only ESA but rose in patients treated concurrently with i.v. iron and ESA. The dysregulation of serum ferritin and TSAT was also shown in a cohort with haematologic and malignant diseases. Twenty-two percent of patients with serum ferritin levels of 100–800 ng/ml and even 24% of those with serum ferritin ≥800 ng/ml had IDA (TSAT <20% and Hb <12 g/dl) [36].

Other markers of iron-restricted erythropoiesis (%HYPO >5%, CHr <26 pg) reflect the outcome of erythropoiesis, especially the rapidly changing CHr [33]. However, advanced equipment and rapid sample processing to avoid expansion of red blood cells are required.

treatment of ID and anaemia

guidelines and regulations

Options for treating anaemia in cancer patients include blood transfusions, ESA therapy, and i.v. iron supplementation. Goals

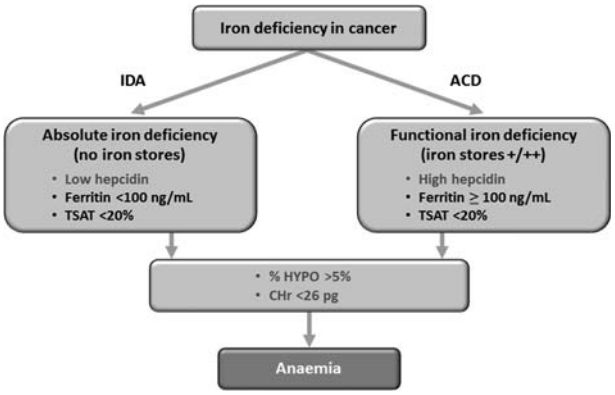

Figure 3. Criteria for diagnosis of iron deficiency in routine practice. Minimal criteria (black) and optimal (grey) work-up for the diagnosis of iron deficiency and distinction between absolute and functional iron deficiency in routine practise. ACD, anaemia of chronic disease; CHr, reticulocyte haemoglobin content; HYPO, hypochromic red cells; IDA, iron deficiency anaemia; TSAT, transferrin saturation.

of anaemia treatment are to improve patients' quality of life and reduce reliance on blood transfusions [5–8] that are still associated with a potential risk for transmission of infectious diseases, transfusion reactions, lung injury, and alloimmunisation [37]. Furthermore, transfusion *per se* may increase the risk of mortality and morbidity including stroke, myocardial infarction, acute renal failure, and recurrence of cancer [38–41].

Transfusion requirements of cancer patients could be reduced with ESAs [42]; however, haematologic response to ESAs is limited (30%–75% of treated patients) [43–45]. Moreover, clinical trials, systematic reviews, and meta-analyses have raised concerns that ESAs increase the risk of thromboembolic events and may increase mortality in patients not receiving chemotherapy, particularly when used off-label [8]. Accordingly, the European Medicines Agency (EMA) revised the target Hb values and highlighted that ESA use should be restricted for clearly symptomatic anaemia [46]. The US Food and Drug Administration (FDA) restricted the indication for ESAs to anaemic patients undergoing myelosuppressive chemotherapy unless cure is the anticipated outcome of chemotherapy [47, 48]. FDA has also implemented a risk evaluation and mitigation strategy requiring training for ESA prescribers and information of patients about ESA-associated risks [49]. Further limits comprise initiation of ESAs in patients with Hb <10 g/dl, dose reductions if Hb increase is ≥1 g/dl within 2 weeks, and avoidance in cancer patients who are not receiving concurrent myelosuppressive chemotherapy [8].

Conversely, current anaemia treatment guidelines in oncology acknowledge that i.v. iron enhances efficacy of ESAs in patients with absolute or functional ID [5–8]. The National Comprehensive Cancer Network (NCCN) suggests consideration of i.v. iron in patients with FID and serum ferritin levels up to 800 ng/ml if TSAT is below 20%; mentioning active infection as only restriction to iron supplementation [7]. Since iron-replete anaemic patients may benefit from i.v. iron supplementation only after initiation of ESA therapy [8], iron status assessment is recommended at baseline, before each cycle of chemotherapy, and throughout any kind of anti-anaemia therapy to ensure timely commencement of iron supplementation.

Oral iron supplementation is only recommended in cases of absolute ID [7]. Although oral iron has been used more commonly than i.v. iron, it is less effective (particularly in ESA-treated cancer patients) and associated with gastrointestinal intolerance and poor compliance [7, 50].

supplementation of ESA therapy with i.v. iron

Seven randomised controlled clinical trials investigating the efficacy of i.v. iron supplementation in ESA-treated anaemic cancer patients have been published between 2004 and 2011 [9–14, 51]. Six studies focused on CIA and one on patients not receiving chemotherapy [12]. All studies except one with an unusual (off-label) dosing schedule [51] showed significant benefit of i.v. iron supplementation. Studies excluding patients with FID at enrolment achieved a 13%–19% absolute increase in response rate [10, 11, 13, 14]. When patients with FID were not excluded from enrolment, absolute increase in response rate was even 34%–43% with i.v. iron compared with no iron [9, 12]. Two studies showed a more rapid response associated with i.v. iron supplementation [12, 14]. This supports the concept that high i.v. iron doses can overcome hepcidin-mediated reduction of iron release from the RES (Figure 2).

In studies including an oral iron arm, i.v. supplementation significantly improved haematologic response compared with oral iron, whereas no significant difference was observed between oral and no iron supplementation [9, 13]. Despite the trials covered different patient populations, i.v. iron formulations, and concomitant chemotherapies, generalisability of the results has been questioned [8]. In particular, the wide range of differences in Hb response rates between treatment and control groups (13%–43%) and a study that seemed to show no benefit of parenteral iron may have raised concerns about the heterogeneity across the trials. However, grouping the results from trials that included patients with FID [9, 12] and trials that focused on iron-replete patients [10, 11, 13, 14] at enrolment showed comparable significantly improved response rates within each of the two populations.

A meta-analysis of eight publications and abstracts on trials comparing i.v. iron with no or oral iron supplementation of ESA therapy ($N = 1555$; including the seven trials mentioned above) showed a 31% increase in the number of patients who achieved a haematopoietic response [95% confidence interval (CI) 1.15–1.49] [52]. Similarly, another meta-analysis of i.v. iron versus no iron supplementation of ESA therapy in seven trials showed a significant 29% increased chance for haematologic response and a 23% reduction in the risk of transfusion (95% CI 0.62–0.97) with i.v. iron supplementation. Comparison of oral versus no iron supplementation in three trials, showed no difference in haematologic response and only a nonsignificant reduction in transfusion risk [53].

dosing of i.v. iron

In the first published trial on i.v. iron supplementation of ESA therapy that included iron-deficient patients, total iron doses

Table 2. Planned total and weekly i.v. iron doses in published randomised controlled trials on i.v. iron supplementation of ESAs in cancer patients[a]

Iron in mg	Auerbach, 2004 [9]	Hedenus, 2007 [12]	Henry, 2007 [13]	Bastit, 2008 [11]	Pedrazzoli, 2008 [14]	Auerbach, 2010 [10]	Steensma, 2011 [51, 54]
Weekly dose	100	100 and 50[b]	125	67	125	133	62.5
Total dose	1000–3000	1100	1000	1000	750	2000	937.5

[a]More detailed information on patient populations, treatments, and outcomes is available as online supplementary material (supplemental Table S1, available at *Annals of Oncology* online).

[b]100 mg iron once weekly from week 0–6 and every second week from week 8–14.

up to 3000 mg were given [9]. In five of the subsequent trials, planned total iron doses were ∼1000 mg (Table 2 and more detailed information in supplemental Table S1, available at *Annals of Oncology* online). One study planned a total dose of 2000 mg iron but the administered mean total iron dose was only 1169 mg [10]. The maximum single doses and minimum infusion times of available parenteral iron preparations (Table 3) depend on their tolerability profiles, mainly determined by the biochemical properties and the manufacturing process. Stable iron complexes can be administered at high doses of 20 mg iron/kg body weight within 15 min (ferric carboxymaltose) to 6 h (iron dextran). Compounds that release iron at a faster rate should be given at a lower pace and dose per infusion (Figure 2).

The impact of dosing schedules beyond recommendations or even off-label has been highlighted by the only study that seemed to show no significant benefit of i.v. iron [51, 55]. In that study, sodium ferric gluconate was given in single doses of 187.5 mg, i.e. 50% above the compound's recommended single dose and known to be associated with a higher incidence and/or increased severity of adverse events (AEs). Conversely, the 3-week administration interval in this study resulted in the lowest calculated weekly iron dose among all published studies (Table 2) [51, 55]. Post hoc analyses suggest that the response to sodium ferric gluconate depended on both the i.v. iron dosage and the hepcidin levels [54, 56]. Patients who received ≥750 mg iron achieved an 80% response rate compared with 67% and 65% in the oral iron and placebo group, respectively. Patients with low or medium hepcidin levels (≤64.3 ng/ml) showed better response rates than patients with high hepcidin levels.

reduction of blood transfusions and ESA doses

A critical aspect in the evaluation of anaemia treatment options such as i.v. iron is the potential to reduce transfusions and/or ESA dose requirements in addition to relief anaemia symptoms. One study that was large enough to uncover potential differences in transfusion rates ($N = 396$ patients) showed a significant reduction of transfusion requirements with i.v. iron versus no or oral iron supplementation [11]. While a prior smaller study suggested a reduction in transfusions compared with the oral or no iron group from week 4 onwards [13], this large study showed a significant reduction of blood transfusions in the i.v. iron treatment group irrespectively whether the entire study period was evaluated ($P = 0.038$) or only the period from week 5 to the end of the study period ($P = 0.005$). The only other study on a comparable scale was stopped prematurely as discussed above [51, 55].

Only one of the trials confirming the efficacy of i.v. iron supplementation reported data on the administered ESA doses [12, 57], showing a dose-sparing effect of i.v. iron from week 5 onwards that reached significance at week 13 ($P = 0.029$). Overall, i.v. iron supplementation of epoetin β reduced the mean cumulative ESA dose by 18% and the mean ESA dose required at the end of the study (week 15) by 25%. Economic analysis revealed that cost savings due to reduced ESA dosage outweighed any additional costs incurred by i.v. iron administration, and an 11% cost benefit could be achieved with i.v. iron supplementation of the ESA regimen [57]. Another study showed that supplementation of darbepoetin alfa with 400 mg i.v. iron provided approximately the same improvement of haematologic response and fatigue scores as ESA dose increase from 300 to 500 μg darbepoetin alfa (all given every 3 weeks) [10].

potential role for i.v. iron as first-line therapy for CIA?

Guidelines recommend treatment of underlying causes of anaemia such as ID before initiation of an ESA. However, studies examining i.v. iron as sole anaemia treatment in cancer patients are only just starting to emerge. Two relevant small ($N = 44$ and 75 patients), controlled, randomised clinical trials have been published. Both studies involved patients with gynaecologic cancers receiving chemotherapy or radiochemotherapy, and in both, i.v. iron supplementation significantly reduced the number of required blood transfusions [15, 16]. In one study, significantly higher Hb levels were observed in the i.v. iron compared with the oral iron group at the end of the study period, although mean Hb levels included data from patients who received transfusions as well as those who did not [15]. The other study, comparing i.v. iron versus no anaemia treatment, achieved a lower rate in transfusions despite a higher baseline proportion of anaemic patients in the study group [16]. Both studies missed to assess iron status parameters such as TSAT and serum ferritin; thus, the proportion of patients with either functional or absolute ID could not be determined.

In the absence of further randomised controlled clinical trials, the trial by Steinmetz et al. [17] may be instructive. This prospective, multicentre parallel group study was designed to investigate the rationale for assigning patients to treatment with either ESA alone, ESA and i.v. iron, or i.v. iron alone based on a diagnostic plot defined by CHr (anaemia defined as

Table 3. Maximum approved single doses for i.v. administration of iron carbohydrate compounds

	Sodium ferric gluconate	Iron sucrose	Ferumoxytol[b]	Iron dextran	Iron isomaltoside	Ferric carboxymaltose
Test dose needed	No	In some countries	No	Yes	No	No
Maximum single infusions dose	125 mg iron[a]	200–500 mg iron	510 mg iron	20 mg iron/kg bw	1000 mg iron (20 mg iron/kg bw)	1000 mg iron (20 mg iron/kg bw)
Minimum infusion time	60 min	30–210 min	17 s	240–360 min	60 min	15 min

[a]Based on results of a recent clinical trial, NCCN guideline changed the recommendation from 200 to 125 mg iron over 60 min [7].
[b]Available only in the United States;
bw body weight; see local summaries of product characteristics for effective updates.

CHr ≤ 28 pg) and the ferritin index (absolute ID defined as ferritin index >2.0 or >3.2 depending whether CRP levels are >5 mg/ml or not). Anaemic patients without ID received ESA treatment only, patients with FID and anaemia received both i.v. iron and ESAs, and patients with absolute ID anaemia received iron only. Hb response rates (Hb increase >1 g/dl from baseline) were comparable between patients receiving i.v. iron alone and those receiving ESA alone. However, 49% of Hb responders to ESA developed ID (as defined by the ferritin index) over the course of the 12-week study. This result, compared with only 19% among patients who received ESA and i.v. iron, suggests that patients identified as iron replete at baseline could also have benefited from i.v. iron supplementation [17].

Notably, a multicentre observational study on the use of ferric carboxymaltose in clinical practice showed a 1.4 g/dl median increase in Hb levels over a 12-week study period (median total iron dose 1000 mg) despite most patients (83%) received ferric carboxymaltose without additional ESA [58].

The efficacy and safety profile of i.v. iron as a monotherapy to treat ID and anaemia has been extensively investigated in patients with other chronic diseases. Several randomised controlled trials have shown that i.v. iron is well tolerated and effective in treating ID anaemia and improving quality of life in patients with inflammatory bowel disease [59, 60]. In patients with chronic heart failure, i.v. iron treatment significantly improved the NYHA functional class (New York Heart Association), physical performance, and quality of life in anaemic and non-anaemic patients [20].

tolerability of i.v. iron in clinical routine

Six of seven randomised controlled clinical trials on i.v. iron supplementation of ESAs in cancer patients did not show a difference in AE rates between i.v. iron and control treatment arms [9–14]. Individual high doses of sodium ferric gluconate that exceeded the recommended dose may have been the reason why one trial reported higher AE rates in the i.v. iron arm [51, 55].

One common prejudice against i.v. iron refers to potential hypersensitivity reactions. However, three analyses evaluating AE reports from 1997 to 2009 have shown that allergic and anaphylactoid reactions, even if rare, are mainly related to iron dextran preparations (Figure 4) [61–63]. Even with low-molecular-weight iron dextrans (numbers from Europe only), the rate of anaphylactic reactions is substantially higher compared with iron sucrose or sodium ferric gluconate (15.6, 0.9, and 0.4 per million 100 mg iron dose equivalents, respectively).

The overall rate of AEs per million 100 mg iron dose equivalents in Europe is 68.9 for low-molecular-weight iron dextrans, 12.8 for iron sucrose, and 3.5 for sodium ferric gluconate [61]. In North America, the AE rate for iron sucrose is lower (4.4), which may be related to the introduction of copies of iron sucrose in Europe but not in the United States. The therapeutic and toxicological equivalence of these copies is currently under discussion and clinical head-to-head comparisons between the copies and the reference product will be needed for clarification [64–66]. Notably, the AE rate for sodium ferric gluconate is higher in North America compared with Europe (12.6 versus 3.5), which may be related to the higher maximum permitted iron dose (125 versus 62.5 mg in most European countries).

Another frequently raised question asks whether i.v. iron increases the risk of infections. To date, no increased rate of infections was observed in patients receiving i.v. iron for treatment of cancer-related anaemia. A study in haemodialysis patients even reported lower rates of infection-related hospitalisations (relative risk 0.54, $P < 0.001$) and mortality (relative risk = 0.61, $P = 0.08$) among haemodialysis patients treated with i.v. iron compared with a general haemodialysis population [67]. However, although not specifically investigated in human studies, animal studies suggest that administration of i.v. iron should be avoided in patients with active sepsis [68].

limitations to the use of i.v. iron in clinical practice

One potential limitation to the use of i.v. iron in cancer patients might be the interaction of iron with certain chemotherapies, in particular anthracyclines and platinum-based therapies [69, 70]. In case of anthracyclines, preclinical data suggest that electron transfer via the superoxide radical results in the release of ferrous iron (Fe^{2+}) from polynuclear ferric oxyhydroxide cores (Fe^{3+}). The released ferrous iron can be reoxidised to ferric iron via the Fenton reaction and thereby generates the highly reactive hydroxide radical [71]. By this means, redox cycling of iron, in particular 'labile' non-transferrin-bound iron, can result in oxidative stress and tissue

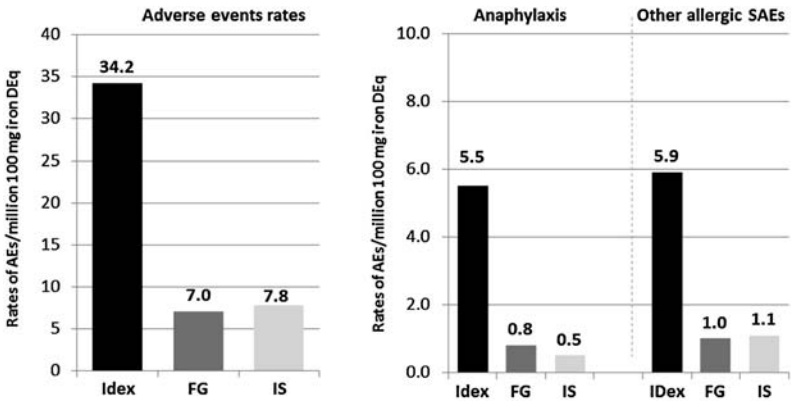

Figure 4. Adverse events rates with parenteral iron preparations in Europe and North America (2003–2009). Rates of total adverse events (AEs) as well as anaphylaxis and other allergic serious AEs per 100 mg iron dose equivalents (DEq) in Europe and North America between 2003 and 2009 [61]. Over the entire observation period, the total of anaphylaxis and other serious allergic AEs was 6- to 10-fold higher with iron dextrans (IDex) than other i.v. iron compounds (iron sucrose, IS; sodium ferric gluconate, FG). (Figure adapted from Bailie et al. *Drug Research* 2011 [61].)

damage. Cardiotoxicity of other chemotherapies seem to be related to other factors such as off-target inhibition of kinases or reduced nitric oxide production rather than interaction with iron [72, 73]. Currently available clinical studies with i.v. iron in cancer patients reported no signs of drug-related iron toxicity and only non-clinical data are available on this topic. Until the availability of such human data, one should consider separating the administration of cardiotoxic cancer treatments and give the i.v. iron at the first visit after administration of a potentially cardiotoxic chemotherapy.

Uncertainty on the potential role of iron in tumour progression largely arises from epidemiological studies showing links between conditions associated with long-term iron overload (e.g. haemochromatosis) and an increased risk of newly induced cancer [71]. However, these conditions do not reflect the situation in anaemic and iron-deficient cancer patients who receive i.v. iron over rather short periods of time for repletion of their iron stores. A potential role of iron in tumour progression of existing tumours has been investigated in non-clinical models. However, these models often used excessive iron doses in iron-replete animals or i.p. iron administration [74, 75]. Until now, no animal model of cancer has been published using i.v. iron administration and thus, the clinical relevance of available non-clinical studies needs to be carefully weighed against the risks that other anti-anaemia treatments, or no treatment present to the patient. Unfortunately, most trials on i.v. iron supplementation of cancer patients were not designed to collect long-term data. One prospective randomised controlled study that is reported in abstract form only monitored patients with lymphoid malignancies who received darbepoetin alfa and i.v. iron following autologous stem cell transplantation. In this preliminary study, 3-year progression-free survival was independent of i.v. iron treatment [76, 77].

concluding remarks

The high prevalence of ID and anaemia in cancer patients suggests that these complications may need more attention in clinical practice. Current guidelines for treating anaemic cancer patients recommend that ID should be considered as underlying cause of anaemia before initiating ESA treatment and acknowledge that i.v. iron supplementation is superior to oral iron. Thorough and regular assessment of cancer patients' iron status (before each chemotherapy cycle) can ensure that these patients receive the most appropriate supportive treatment for their needs. Among different potential markers of iron status, TSAT has been suggested as reliable marker that allows diagnosis of both absolute and FID without the need for additional assessments of liver function or inflammatory parameters.

Published randomised controlled trials show that i.v. iron enhances response rates to ESA therapy and may be effective in reducing ESA doses and blood transfusion requirements, even if long-term safety remains to be examined. Available early reports on the use of i.v. iron as first-line anaemia therapy suggest that some patients could benefit from i.v. iron even without concomitant ESA. However, larger randomised controlled studies with long-term follow-up are necessary to confirm long-term efficacy and safety.

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