Increased Efficacy of Anaemia Treatment in Cancer

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Abstract
Approximately 75% of patients receiving chemotherapy for cancer will become anaemic during the course of their treatment. Many of these patients will be symptomatic. Correction of the anaemia with erythropoiesis-stimulating agents (ESAs) improves the haemoglobin concentration in more than half of these patients. Several recent trials have suggested that the rate and speed of haemoglobin response can be improved if intravenous (IV) iron is given in combination with the ESA, and also that the IV iron preparations are safe.

Keywords
Cancer-related anaemia, functional iron deficiency, erythropoiesis-stimulating agents, epoietin, darbepoietin, intravenous iron

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Cancer-related anaemia (CRA) is a common problem that is reported in up to 75% of patients receiving chemotherapy. Randomised trials of erythropoiesis-stimulating agents (ESAs) report an improvement in the haemoglobin concentration of >2g/dl in 50–70% of patients, which results in a reduction in the need for transfusion and an improvement in quality of life. However, there have been a number of safety concerns over the use of ESAs in treating CRA. A recent updated Cochrane meta-analysis reviewed the effects of epoietin alpha and beta and darbepoietin alpha in 53 trials in 13,933 patients. ESAs increased on-study deaths (hazard ratio [HR] 1.17, 95% confidence interval [CI] 1.07–1.30) and decreased overall survival (HR 1.06, CI 1.1–1.12). In 38 trials of 10,441 patients restricted to those receiving chemotherapy, ESAs increased on-study deaths (HR 1.10, CI 0.98–1.24) and decreased overall survival (HR 1.04, CI 0.97–1.11). These differences were not significant. The reasons for the increased mortality are not clear, but it probably reflects an increased risk of thrombosis. A direct effect of ESAs on tumour progression is also possible. These safety concerns have resulted in a tightening of the guidelines for ESA use in patients with cancer.

Causes of Anaemia in Patients with Cancer
The aetiology of CRA is multifactorial. It is important to look for blood loss, haemolysis, bone marrow infiltration by tumour cells and nutritional deficiencies, but in most cases the anaemia is caused by the cytokine-mediated anaemia of chronic disease compounded by the myelotoxic impact of chemo- and/or radiotherapy. It has been postulated that at least three pathological processes are involved: shortened erythrocyte survival, failure of the bone marrow to increase red cell production to compensate for this and impaired release of iron from the reticuloendothelial system. The anaemia of chronic disease is characterised by low serum iron in the presence of adequate iron stores (functional iron deficiency). Functional iron deficiency, where there is restricted iron release from macrophages in the reticuloendothelial system, may be a major reason for a response rate of only 50–70% in ESA-treated patients. Since the discovery of the iron-regulatory peptide hepcidin, our understanding of the biology of anaemia of chronic disease has improved greatly. Hepcidin is upregulated in the setting of chronic inflammation and cancer, resulting in its increased synthesis in the liver. By degrading ferroportin, hepcidin decreases iron absorption from the gastrointestinal tract and decreases the accessibility of stored iron from macrophages.

Iron-restricted erythropoiesis can be aggravated when ESA treatment increases the demand for iron transport to the bone marrow. It is likely that in conditions of increased hepcidin synthesis, functional iron deficiency will restrict the erythroid response to ESAs; it is also likely that oral iron will be absorbed poorly and that intravenous (IV) iron preparations may overcome the block. In patients treated with ESAs for the anaemia associated with chronic kidney disease, the response rate improved when IV rather than oral iron supplements were given and often allowed a reduction in the ESA dose. IV iron is routinely used in ESA-treated patients with chronic kidney disease, and this practice is endorsed in international guidelines. During the last six years, five randomised trials of ESAs plus or minus IV iron have shown an improvement in the response rate in the IV iron groups.

Randomised Trials of Erythropoiesis-Stimulating Agents with and without Intravenous Iron in Cancer
The first study, published by Auerbach et al. in 2004, randomised 157 anaemic cancer patients who were receiving weekly epoietin alpha to no iron, oral iron, weekly IV low-molecular-weight iron dextran or IV dextran total dose infusion. Eligible patients had a serum ferritin ≤450pmol/l or ≤675 pmol/l with transferrin saturation of ≤19%. Patients were followed for six weeks. Response rates were significantly better in the IV iron groups, with 68% of these patients achieving a haemoglobin
to a doubling of the darbepoietin dose than those in the no iron group. Another interesting finding was that non-responding patients included at study entry. A second study addressing some of these matters was undertaken by Henry et al., who randomised 187 patients with CRA receiving epoietin alpha to no iron, oral iron or once-weekly IV ferric gluconate. Inclusion criteria included serum ferritin >100ng/ml or transferrin saturation >15%. Patients were followed for 12 weeks and treated for eight of those weeks. Only 12% of the randomised patients were evaluable. The haemoglobin response was 73% for ferric gluconate, 46% for oral iron and 41% for no iron. More than 90% of the study’s patients had transferrin saturations >20% and serum ferritin levels >100ng/ml, ruling out the possibility that iron deficiency accounted for the poor response in the epoietin only group. Of particular note, giving oral iron did not improve the response rate compared with the no iron group.

Hedenus et al. examined the addition of IV iron to epoietin beta in anaemic patients with lymphoproliferative malignancies who were not receiving chemotherapy. All of the patients had adequate marrow iron stores. Sixty-seven patients were randomised to receive epoietin beta only or epoietin beta plus IV iron sucrose for 14 weeks of the 16-week study period. Haemoglobin response was achieved by significantly more patients in the iron (93%) versus no iron group (53%). The time to achieve this response was also shorter in the iron group. Interestingly, from week five onwards there was an increasing difference in the mean epoietin dose in favour of the iron group, with an approximately 25% lower dose in the iron group by week 15. This corresponds with data from haemodialysis trials. A further aim of this trial was to examine iron kinetics in an iron-replete population. In the no iron group there was a rapid decrease in mean serum ferritin at week one, which continued to the end of the study. By contrast, the mean ferritin level almost doubled in the iron group. In the no iron group, 87% had transferrin saturations <20% during >75% of the study, indicating the development of functional iron deficiency. This suggests that better iron availability leads to an improved haemoglobin response.

A more recent 16-week open-label, randomised trial by Bastit et al. included 396 patients with non-myeloid malignancies and chemotherapy-induced anaemia who received darbepoietin alpha every three weeks along with standard care (no or oral iron) or with weekly or twice-weekly IV iron sucrose or ferric gluconate. Patients with transferrin saturations <15% and serum ferritin <10ng/ml were excluded. More than 35% of the patients had evidence of functional or absolute iron deficiency. The haematopoietic response was significantly higher in the IV iron group, which also had a more rapid haemoglobin response. This trial showed a statistically significant reduction in transfusion requirements in the IV iron group. One may criticise this study for including iron-deficient patients, but this is the largest study to date to show the positive relationship between IV iron and ESA therapy in CRA. Pedrazzoli et al. studied 149 iron-replete anaemic patients with solid tumours receiving chemotherapy randomised to darbepoietin alpha weekly for 12 weeks with or without IV iron sucrose for the first six weeks. Inclusion criteria required serum ferritin levels >100ng/ml and transferrin saturations >20%, ruling out absolute iron deficiency and functional iron deficiency. Seventy-seven per cent of the IV iron group responded versus 62% in the no iron group. Another interesting finding was that non-responding patients at four weeks in the iron group were far more likely to respond to a doubling of the darbepoietin dose than those in the no iron group (68.2% response versus 32%). This suggests that avoiding the development of functional iron deficiency in these iron-replete patients leads to a subsequent haemoglobin response.

Safety of Intravenous Iron Preparations

Parenteral iron preparations acquired a bad reputation because of the serious adverse events, in particular anaphylaxis, reported with the use of high-molecular-weight iron dextran. A study in renal dialysis patients receiving parenteral iron preparations showed that the risks of serious adverse events were 0.6, 0.9, 3.3 and 11.3 per million for iron sucrose, sodium ferric gluconate complex, low-molecular-weight iron dextran and higher-molecular-weight iron dextran, respectively. Intramuscular iron has no therapeutic advantages over IV iron and has the disadvantage of pain at the injection site and may cause skin staining. There are also occasional reports of sarcomas developing at the site of intramuscular iron injections in animals (and possibly humans) with high-molecular-weight iron dextran. In the trials described above in patients with cancer, IV iron was not associated with an increased incidence of adverse events compared with oral iron.

Post-marketing surveillance reports have suggested a rate of hyper-reactivity reactions of 3.3 episodes per million for ferric gluconate and 2.6 episodes per million for iron sucrose. None of these events was fatal. Hypotension, nausea and back pain seemed to occur more commonly during iron infusions when the recommended dose and infusion rate were exceeded. Concerns about an adverse effect of IV iron on cardiovascular disease in patients with end-stage renal disease are based on concerns about an increase in oxidative stress in iron-treated patients. No evidence for an increase in risk has been demonstrated, although larger studies with longer follow-up are needed.

Conclusions

Anaemia is a common problem in patients with cancer being treated with chemotherapy, and the combination of IV iron with an ESA increases the haemoglobin response rate compared with treatment with an ESA alone or in combination with oral iron. Indeed, there is no evidence that the addition of oral iron is of any value. There are important concerns about the safety of ESAs. However, in the Cochrane review there was no statistically significant impact of ESAs on overall survival in cancer patients being treated with chemotherapy, and their use is considered valid as long as they are used within their licensed indications. ESAs remain an important part of anaemia management in patients with the symptomatic anaemia of cancer who are receiving chemotherapy, and IV iron enhances the response rate.


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