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ORIGINAL ARTICLE

Efficacy of Intravenous Iron in Cancer Patients with Moderate to Severe Iron Deficiency Anaemia

W Chan, FAS Lee, WWY Tin, SF Yip, FCS Wong

Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong

ABSTRACT

Introduction: *Iron deficiency anaemia is common in patients with cancer. Intravenous iron is approved for treatment of iron deficiency anaemia when oral iron preparations are ineffective. Few data are available on the rapidity of haemoglobin correction in patients with cancer and moderate to severe iron deficiency anaemia who are given intravenous iron.*

Methods: *We retrospectively reviewed the efficacy and safety of ferric carboxymaltose (FCM) in cancer patients with iron deficiency anaemia who were treated in our centre from January to June 2019. The primary endpoint was the rise in haemoglobin levels at day 7, day 14, and day 28 after the first dose of FCM. The secondary endpoints included the change in iron profile, the sustainability of haemoglobin response at day 60, and the changes in patients' transfusion requirements following FCM.*

Results: *The mean baseline haemoglobin level of the 34 patients given FCM during this period was 7.8 g/dL. The mean haemoglobin rise at day 7, day 14, and day 28 was 0.5 g/dL, 1.1 g/dL, and 2.1 g/dL, respectively. The rise in haemoglobin level was sustainable at day 60 and accompanied by rises in ferritin and iron saturation ($p < 0.001$). There was a statistically significant reduction in patients' transfusion requirements ($p = 0.016$). No hypersensitivity reaction or abnormality of vital signs was reported.*

Conclusions: *In patients with cancer and moderate to severe iron deficiency anaemia, FCM induced a prompt rise in haemoglobin levels. This treatment may be a viable option for patients with iron deficiency anaemia who may otherwise require transfusion.*

Key Words: *Blood transfusion; Ferric Compounds; Neoplasms*

Correspondence: *Dr W Chan, Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong*
Email: ac_wai@hotmail.com

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Ethics Approval: This study was approved by the Research Ethics Committee of North Territory West Cluster, Hospital Authority (Ref NTWC/REC/19055). The need for patient consent was waived owing to the retrospective nature of the study.

中文摘要

靜脈注射鐵劑對中重度缺鐵性貧血癌症患者的療效

陳偉、李安誠、佃穎恩、葉仕輝、黃志成

引言：缺鐵性貧血在癌症患者中很常見。當口服鐵劑無效時，靜脈注射鐵劑可用於治療缺鐵性貧血。有關中重度缺鐵性貧血癌症患者在靜脈注射鐵劑後的血紅蛋白校正的快速性尚無數據。

方法：我們回顧分析靜脈注射鐵劑羧甲基麥芽糖（FCM）在缺鐵性貧血癌症患者中的有效性和安全性。患者於2019年1月至2019年6月接受治療，研究的主要終點是注射第一劑FCM後第7天、第14天和第28天的血紅蛋白升幅。次要終點包括鐵譜的變化、第60天時血紅蛋白反應的可持續性，以及FCM後輸血需求的變化。

結果：34名患者在研究期間接受FCM。平均基線血紅蛋白為7.8 g/dL。第7天、第14天和第28天的血紅蛋白平均升幅分別為0.5 g/dL、1.1 g/dL和2.1 g/dL。血紅蛋白的增幅在第60天是可持續的，伴有鐵蛋白和鐵飽和度的增加（$p < 0.001$）。輸血量顯著減少（$p = 0.016$）。患者沒有出現過敏反應或生命體徵異常。

結論：對於中重度缺鐵性貧血癌症患者，FCM可迅速增加血紅蛋白。對於可能需要輸血的缺鐵性貧血患者，FCM是一種可行的治療選擇。

INTRODUCTION

Iron deficiency has been reported to be present in up to 42.6% of patients with cancer.[1] Randomised controlled trials have shown that intravenous iron was superior to oral iron at correcting iron deficiency anaemia in patients with renal failure, heavy uterine bleeding, and inflammatory bowel disease.[2-4] A meta-analysis primarily involving patients with non-malignant causes of iron deficiency anaemia suggested that intravenous iron may reduce patients' transfusion needs.[5]

Patients with cancer have distinct patterns of iron metabolism and complex pathogenesis of iron deficiency anaemia.[6] In patients with cancer, iron deficiency can be caused by tumour bleeding, poor oral intake or impaired iron absorption. Two large prospective observational studies showed that intravenous iron could correct iron deficiency anaemia effectively in patients with cancer.[7,8] However, previous studies in patients with cancer focused on anaemia with baseline haemoglobin levels of 9 to 11 g/dL.[7-12] In addition, the majority of the aforementioned studies assessed the trend of haemoglobin levels at a monthly interval and therefore did not provide much information about haemoglobin levels during the first 4 weeks after treatment.

The evidence for intravenous iron in patients with cancer and more severe anaemia (e.g., haemoglobin 7-9 g/dL) is more limited. These patients may have higher rates of bleeding and more prominent anaemic symptoms that require rapid correction of haemoglobin levels. Data on the rate of haemoglobin response following intravenous iron administration in these patients are lacking. Blood transfusion can correct anaemia quickly, but it is limited by supply, carries risk, and may be associated with poorer oncological outcomes.[13] It is not known whether intravenous iron can correct anaemia rapidly to avoid transfusion in patients with lower baseline haemoglobin levels.

Ferric carboxymaltose (FCM) is a form of intravenous iron. It was approved by the United Kingdom Medicines and Healthcare products Regulatory Agency in 2007 for iron deficiency anaemia when oral iron preparations are ineffective or cannot be used. Since January 2019, our department has been using FCM to correct iron deficiency anaemia. The aim of this study was to determine the efficacy of FCM in patients with cancer and moderate to severe anaemia, particularly during the first 4 weeks of treatment. Use of intravenous iron is part of the patient blood management approach to reduce transfusion and improve clinical outcomes.[14]

METHODS

Study Design and Population

This single-centre retrospective study included all

consecutive patients with cancer who received at least one dose of FCM between 1 January 2019 and 30 June 2019 in our centre. The study was approved by the Research Ethics Committee of North Territory West Cluster, Hospital Authority (Ref NTWC/REC/19055). The STROBE guidelines were used to ensure the reporting of this study.[15]

In our centre, clinicians prescribed FCM and arranged follow-up blood tests according to our department protocol. The eligibility criteria in our department protocol were Karnofsky Performance Status ≥60, iron saturation <20% with ferritin <220 pmol/L, and either haemoglobin <8 g/dL or haemoglobin 8 to 9 g/dL with at least one of the following: active bleeding, on regular proton pump inhibitors/histamine 2 blockers, or failure of oral iron to induce adequate haemoglobin rise. These criteria were devised to select patients in whom oral iron would likely be ineffective. Patients with low haemoglobin (<8 g/dL) or active bleeding with stable haemodynamics require rapid replacement of the iron store, which could not be achieved by oral iron. Absorption of oral iron is enhanced by gastric pH and is reduced by medications that inhibit gastric acid release. The exclusion criteria included allergy to intravenous iron, active infection, asthma, allergy to more two or more drugs, inflammatory joint disease, cirrhosis, and hypophosphataemia at baseline.

Patients receiving FCM had baseline and follow-up blood tests according to our department protocol. At baseline, blood tests including complete blood count (CBC), reticulocyte count, liver and renal function tests, and levels of calcium, phosphate, iron saturation, and ferritin were performed. At 1 week and 2 weeks after the first dose of FCM, CBC and reticulocyte count were repeated. At 4 weeks after the first dose of FCM, blood tests including CBC, reticulocyte count, and calcium, phosphate, iron saturation, and ferritin levels were repeated. Calcium and phosphate levels were measured at baseline and at day 28 because intravenous iron is known to cause hypophosphataemia by increasing urinary phosphate excretion.[16] Thereafter, the frequency of blood tests was decided by the treating clinician. Transfusion of packed cells was arranged by the treating clinician, as clinically indicated.

The dose of FCM was determined according to the patient's body weight. A single dose of 500 mg was given to patients whose body weight was <40 kg. Two doses of 750 mg one week apart were given to patients whose body weight was 40 to 70 kg. Two doses of 1000 mg one week apart were given to patients whose body weight was >70 kg. Oral iron was withheld for at least 4 weeks after intravenous iron administration. The presence of any anaemic symptoms, including dizziness, fatigue, shortness of breath or palpitation was assessed at baseline and at follow-up visits. The interval of follow-up visits was decided by the treating clinicians.

Parameters

Baseline characteristics including age, gender, performance status, cancer type, treatment intent (curative or palliative), and concurrent cancer treatment (e.g., chemotherapy, target therapy, radiotherapy) were accessed from the clinical notes. The dose and date of FCM administration were retrieved from the drug dispensing history within the electronic patient record.

The blood results at baseline, day 7, day 14, and day 28 were evaluated to investigate the changes in haemoglobin, mean corpuscular volume, reticulocyte count, iron saturation, ferritin, and phosphate levels. Blood results were recorded as corresponding to day 7, day 14, and day 28 if they were obtained at 7±3 days, 14±4 days, and 28±4 days after the first dose of intravenous FCM, respectively. When several blood results from a particular week were available, the results closest to the pre-determined dates (i.e., day 7, day 14, and day 28) were used. These blood results were retrieved from the electronic patient record.

To assess the sustainability of haemoglobin response, the patients' haemoglobin levels at day 60 (defined as 60±10 days after the first dose of FCM) were recorded.

The consultation notes were reviewed to assess any reported side effects and improvement of anaemic symptoms including dizziness, palpitation, fatigue, and shortness of breath. Information regarding transfusions was assessed using the Clinical Data Analysis and Reporting System, which was able to retrieve all of the patients' blood transfusion history given in hospitals under the Hospital Authority, Hong Kong. The transfusion history was verified by reviewing the consultation notes.

Objectives

The primary objective was to evaluate the haemoglobin increase from baseline to day 7, day 14, and day 28. The secondary objectives were to investigate the sustainability of haemoglobin at day 60, the change in

iron profile, the safety profile of FCM, and its effects on the patients' transfusion requirements. Each patient's transfusion requirement was assessed by comparing the number of packed cells transfused within 60 days before and 60 days after FCM.

Confounding Factors

Transfusion could be an important confounding factor that modulates changes to haemoglobin levels. Patients who received transfusions before day 28 were excluded from analysis of the haemoglobin trend, change of iron profile, and improvement of anaemic symptoms. Transfusion can raise haemoglobin levels, alter the iron profile, and improve anaemic symptoms. If patients who received transfusions were not excluded, this would overestimate the effects of FCM on the above parameters.

Patients who received haemostatic interventions (e.g., radiotherapy, embolisation) within 60 days of the first dose of FCM were excluded from analysis of the transfusion requirement. Haemostatic radiotherapy to the tumour or embolisation of bleeding vessels could alter the bleeding rate and be a significant confounding factor that modulates the change in transfusion requirements after FCM.

Statistical Analysis

Categorical data are summarised as number and percentage. Continuous variables are presented as mean±standard deviation unless otherwise stated.

Paired-samples *t* tests were used to assess the changes in haemoglobin levels, iron profile, and number of packed cells transfused before vs after FCM.

Patients with missing data for any of the primary or secondary objectives for any reason, including death, were excluded from analysis for that study objective.

RESULTS

Patient Characteristics

All of the 34 patients given FCM from January to June 2019 were included for analysis. Their baseline characteristics are shown in Table 1. The mean baseline haemoglobin level was 7.8 g/dL.

Among the patients, 82.4% received 1500 mg divided into two infusions. The other doses given included a single infusion of 500 mg (8.8%), a single infusion of 750 mg (6%), and 2000 mg divided into two infusions (3%).

Table 1. Baseline characteristics (n=34).*

Age, y	72.1±14.6
Male, %	23 (67.6%)
Karnofsky Performance Status, median (range)	70 (60-90)
Body weight, kg	54.1±9.9
Cancer type	
Upper gastrointestinal tract	32.3%
Lower gastrointestinal tract	29.4%
Hepato-pancreaticobiliary tract	8.9%
Breast	8.9%
Urologic	8.9%
Others	11.8%
Concurrent cancer treatment	
Palliative care alone	55.9%
Radical or adjuvant chemotherapy	8.9%
Palliative chemotherapy	23.5%
Targeted therapy	5.7%
Concurrent chemo-irradiation	2.9%
Baseline blood parameters	
Haemoglobin, g/dL	7.8±0.7
Mean corpuscular volume, fL	78.4±10.6
Iron saturation	7.0%±3.7%
Total iron binding capacity, μmol/L	52.4±13.8
Ferritin, pmol/L	88.3±61.3
Serum phosphate, mmol/L	1.05±0.19
Clinical features	
Active bleeding	44%
On proton pump inhibitors	41.1%
On histamine 2 blockers	8.8%
Prior oral iron (within 4 weeks)	38.0%

* Data are presented as No. (%) or mean±standard deviation, unless otherwise stated.

Efficacy

After patients who received transfusions (n = 6) or died (n = 3) within 28 days of the first dose of FCM were excluded, data from 25 patients could be analysed for changes of haemoglobin and iron profile. They all had CBC available at day 0, day 7, day 14, and day 28. The median intervals between the dates of the 'day 0', 'day 7', and 'day 14' CBC time points and that of the baseline CBC were 7 days (range, 7-10 days), 14 days (range, 13-18 days), and 28 days (range, 26-32 days), respectively. The trend of mean haemoglobin levels with 95% confidence intervals is shown in Figure 1. Compared with day 0, the mean haemoglobin level had increased by 0.5 g/dL at day 7 ($p < 0.01$), 1.1 g/dL at day 14 ($p < 0.001$), and 2.1 g/dL at day 28 ($p < 0.001$).

All 25 patients had baseline iron profiles including iron saturation and ferritin available. Of the patients, 92% had a repeated iron profile and ferritin available at 28 days±4 days after the first dose of FCM. There was a statistically significant ($p < 0.001$) increase in iron saturation and ferritin at that time point. The mean iron saturation and ferritin levels at baseline and day 28 are shown in Table 2.

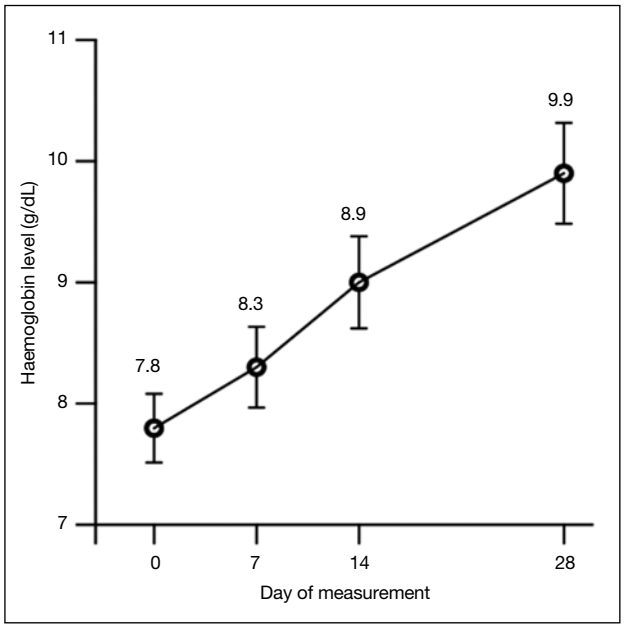

Figure 1. Change in haemoglobin level (mean with 95% confidence interval) during the first 28 days (n = 25).

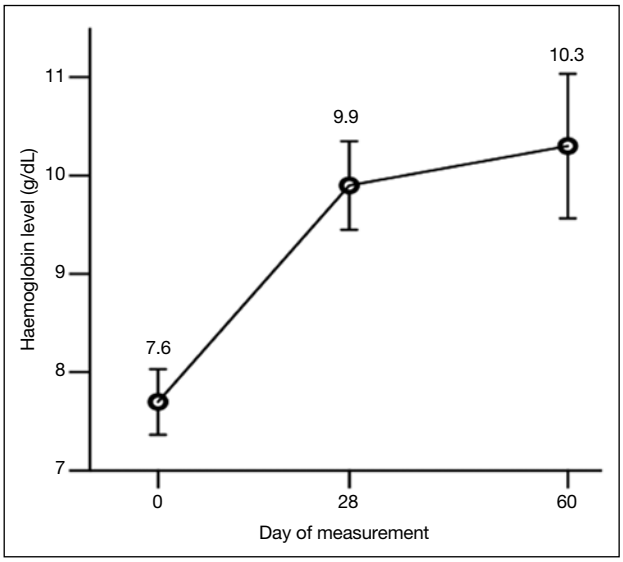

Figure 2. Sustainability of haemoglobin level (mean with 95% confidence interval) at day 60 (n = 21).

Table 2. Change of iron profile.*

	Baseline	Day 28	p Value
Iron saturation	6.5%	23.2%	p < 0.001
Ferritin, pmol/L	78.9	1762.3	p < 0.001

* Data are presented as mean.

Table 3. Number of packed cells transfused within 60 days before and after ferric carboxymaltose (FCM).

	Within 60 days before FCM	Within 60 days after FCM
Patient A	2	0
Patient B	3	2
Patient C	3	0
Patient D	1	0
Patient E	1	0

Among the six patients who received transfusion within 28 days of the first dose of FCM, five had upper gastrointestinal tract tumours with bleeding. They were admitted for haematemesis or melaena with haemoglobin level drops that required transfusion. One of them underwent embolisation of the bleeding vessel by an interventional radiologist after transfusion to stop the massive bleeding. Another patient had haemoperitoneum that required an emergency angiogram and transfusion.

There was a sustainable rise of haemoglobin level at 60±10 days after the first dose of FCM. Among the 25 patients included above, two received transfusions and one died between day 28 and day 60. One patient did not have a haemoglobin level check at day 60. The two patients who had transfusions between day 28 and day 60 had tumour progression in the upper gastrointestinal tract that caused increases in tumour bleeding. They both had metastatic cancer without effective cancer treatment. The haemoglobin levels of the remaining 21 patients were analysed to assess the sustainability of FCM-induced haemoglobin rise. Their mean haemoglobin levels with 95% confidence intervals at baseline, day 28, and day 60 are shown in Figure 2.

There was also a statistically significant (p = 0.016) reduction in the number of packed cells transfused following FCM administration. After excluding patients who received haemostatic intervention, the numbers of packed cells transfused in each patient within 60 days before and after FCM are shown in Table 3.

In total, 88% of patients reported improvement of at least one of their anaemic symptoms.

Safety

No hypersensitivity reactions or abnormalities of vital signs were reported following FCM administration.

All patients had baseline phosphate levels available. Phosphate levels measured at 28±4 days after the first

dose of FCM were available for 20 patients. There was a statistically significant ($p = 0.002$) reduction of phosphate levels from baseline to day 28 (from 1.01 mmol/L to 0.72 mmol/L). No clinical symptoms attributed to hypophosphataemia were reported.

DISCUSSION

Our study showed a prompt response in the haemoglobin levels of patients with cancer and moderate to severe anaemia who were given FCM. Compared with baseline, their haemoglobin levels rose by 0.5 g/dL and 1.1 g/dL at day 7 and day 14, respectively. By day 28, the haemoglobin rise reached 2.1 g/dL and was sustained at 60 days after FCM. This haemoglobin response was accompanied by a statistically significant improvement of the iron profile and a corresponding reduction in transfusion requirements. The patients' mean baseline haemoglobin level was 7.8 g/dL, which was close to the transfusion threshold in clinical practice.

The results of the present study suggest that intravenous iron could be a viable treatment option for patients with cancer and symptomatic iron deficiency anaemia who may otherwise require transfusions. This result is particularly meaningful in the context of a worldwide shortage of blood products. The demand for donated blood has been rising worldwide as a result of the ageing population.[17] The use of intravenous iron may help to avoid the cost and risks of transfusion of donated blood, which is limited in supply.

The rapid rise of haemoglobin levels induced by intravenous iron could be particularly useful in patients who will receive radical radiotherapy. Anaemia has been shown to correlate with poor tumour oxygenation and may confer radioresistance.[18] Consequently, before radical radiotherapy, some institutions (including ours) arrange transfusions of packed cells for patients whose haemoglobin levels are <10 g/dL.[19] As intravenous iron can raise haemoglobin levels promptly, patients with cancer and iron deficiency anaemia can be treated with intravenous iron while radiotherapy planning is in progress. This may obviate or reduce the need for transfusions to top up haemoglobin to the target level, particularly if the period between intravenous iron infusion and the start of radiotherapy is more than 2 weeks. If an immediate rise of haemoglobin is desired, transfusion followed by correction of the iron deficiency by either the oral or intravenous route can be considered.

Of our patients, 24% required transfusions within the 60 days after FCM. Most of them had tumours in the upper gastrointestinal tract that were causing significant bleeding. In these patients, the rate of blood loss likely exceeded the rate of restored erythropoiesis following intravenous iron replacement. This highlighted the importance of control of the bleeding source, for instance by haemostatic radiotherapy or embolisation of the bleeding vessel.

Our study has several strengths. First, the vast majority of our patients had critical haematological parameters (including CBC and iron profile) at baseline and at scheduled intervals. For instance, all of our patients had baseline haemoglobin, iron saturation, and ferritin levels available. In comparison, among the three largest reported series of patients with cancer who received FCM, baseline iron saturation and ferritin levels were only available in 54% to 74% and 54% to 57% of patients, respectively.[7,8,11] Excluding patients who died or received transfusions, all of our patients underwent assessment of haemoglobin levels at the pre-specified intervals in the first 4 weeks. The relative completeness of the data enhanced the study's statistical precision.

Second, all patients in our study were selected to receive FCM based on our department protocol's pre-specified eligibility criteria. Our eligibility criteria for FCM, described above, targeted patients in whom oral iron would likely be ineffective. The eligibility criteria for intravenous iron applied by the two large multi-centred series of FCM in patients with cancer were not well defined.[7,8] The lack of consistent eligibility criteria in those multi-centred studies likely reflected variation in the study centres' practices of selecting patients for intravenous iron. Our results, based on the clear, pre-specified eligibility criteria outlined in our department protocol, can be informative to other oncology departments that are planning to incorporate the use of intravenous iron into their practice.

Our study also has some weaknesses. First, there could be confounding factors that affect the changes in haemoglobin levels and transfusion requirements. These confounding factors could include tumour progression or shrinkage, which could lead to variability of the bleeding rate, and concurrent myelosuppressive cancer treatment. The lack of a comparator or a randomised design could make interpretation of the haemoglobin rise difficult. Consequently, the changes in haemoglobin levels observed in our study might not be fully attributable to the effects of FCM.

Second, oral iron is a cheap and convenient treatment for iron deficiency anaemia. Our study does not answer the question of how to select patients for intravenous iron. Randomised trials comparing intravenous iron with oral iron, using pre-specified eligibility criteria, are needed to guide decisions about patient selection for intravenous iron. A published randomised controlled trial failed to show the superiority of intravenous iron over oral iron in patients with cancer.[20] This result could be related to the eligibility criteria of that trial, which included all patients with cancer and iron deficiency anaemia who had haemoglobin levels <12 g/dL. The superiority of intravenous iron over oral iron would likely be most obvious in patients who showed unsatisfactory response to oral iron, such as those fulfilling our study's eligibility criteria.

Third, the assessment of anaemic symptoms in our patients was performed by the treating clinicians only. Assessment of anaemic symptoms and quality of life is best performed by a validated patient-reported outcome instrument. Examples of such instruments to assess iron deficiency anaemia include the Functional Assessment of Cancer Therapy–Anaemia and the 36-item Short Form Health Survey.[21] Without such instruments, our assessment of anaemic symptoms is less reliable.

Our study's external validity is limited by its small sample size and the lack of a comparator group. Nevertheless, the encouraging result of rapid haemoglobin rise following intravenous iron administration can still be informative to oncologists, who might want to consider alternatives to blood transfusion.

CONCLUSION

In patients with cancer and symptomatic iron deficiency anaemia, FCM can correct iron deficiency, raise haemoglobin levels promptly, and reduce transfusion requirements. This may reduce the demand for blood products and avoid risks related to blood transfusion.

REFERENCES

1. Ludwig H, Müldür E, Endler G, Hübl W. Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia. Ann Oncol. 2013;24:1886-92.
2. Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. Am J Kidney Dis. 2016;68:677-90.
3. Van Wyck DB, Mangione A, Morrison J, Hadley PE, Jehle JA, Goodnough LT. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. Transfusion. 2009;49:2719-28.
4. Lindgren S, Wikman O, Befrits R, et al. Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: a randomized, controlled, evaluator-blind, multicentre study. Scand J Gastroenterol. 2009;44:838-45.
5. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. BMJ. 2013;347:f4822.
6. Busti F, Marchi G, Ugolini S, Castagna A, Girelli D. Anemia and iron deficiency in cancer patients: role of iron replacement therapy. Pharmaceuticals (Basel). 2018;11:94.
7. Steinmetz T, Tschechne B, Harlin O, et al. Clinical experience with ferric carboxymaltose in the treatment of cancer- and chemotherapy-associated anaemia. Ann Oncol. 2013;24:475-82.
8. Toledano A, Luporsi E, Morere JF, et al. Clinical use of ferric carboxymaltose in patients with solid tumours or haematological malignancies in France. Support Care Cancer. 2016;24:67-75.
9. Abdel-Razeq H, Abbasi S, Saadi I, Jaber R, Abdelelah H. Intravenous iron monotherapy for the treatment of non-iron-deficiency anemia in cancer patients undergoing chemotherapy: a pilot study. Drug Des Devel Ther. 2013;7:939-44.
10. Calleja JL, Delgado S, del Val A, et al. Ferric carboxymaltose reduces transfusions and hospital stay in patients with colon cancer and anemia. Int J Colorectal Dis. 2016;31:543-51.
11. Coussirou J, Debourdeau A, Stancu A, et al. Impact of ferric carboxymaltose on the evolution of hemoglobin and ECOG performance status in iron-deficient patients with solid tumors: a 3-month follow-up retrospective study. Support Care Cancer. 2018;26:3827-34.
12. Lima J, Gago P, Rocha M, et al. Role of intravenous iron in the treatment of anemia in patients with gastrointestinal tract tumors undergoing chemotherapy: a single-center, observational study. Int J Gen Med. 2018;11:331-6.
13. Goubran HA, Elemary M, Radosevich M, Seghatchian J, El-Ekiaby M, Burnouf T. Impact of transfusion on cancer growth and outcome. Cancer Growth Metastasis. 2016;9:1-8.
14. Franchini M, Marano G, Veropalumbo E, et al. Patient blood management: a revolutionary approach to transfusion medicine. Blood Transfus. 2019;17:191-5.
15. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344-9.
16. Hardy S, Vandemergel X. Intravenous iron administration and hypophosphatemia in clinical practice. Int J Rheumatol. 2015;2015:468675.
17. Ali A, Auvinen MK, Rautonen J. The aging population poses a global challenge for blood services. Transfusion. 2010;50:584-8.
18. Becker A, Stadler P, Lavey RS, et al. Severe anemia is associated with poor tumor oxygenation in head and neck squamous cell carcinomas. Int J Radiat Oncol Biol Phys. 2000;46:459-66.
19. Harrison LB, Chadha M, Hill RJ, Hu K, Shasha D. Impact of tumor hypoxia and anemia on radiation therapy outcomes. Oncologist. 2002;7:492-508.
20. Birgegård G, Henry D, Glaspy J, Chopra R, Thomsen LL, Auerbach M. A randomized noninferiority trial of intravenous iron isomaltoside versus oral iron sulfate in patients with nonmyeloid malignancies and anemia receiving chemotherapy: the PROFOUND trial. Pharmacotherapy. 2016;36:402-14.
21. Strauss WE, Auerbach M. Health-related quality of life in patients with iron deficiency anemia: impact of treatment with intravenous iron. Patient Relat Outcome Meas. 2018;9:285-98.