Clinical Study

Efficacy of Ferric Carboxymaltose in Anaemia of Malignancy — A Pilot Study

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Abstract

Introduction: Anaemia is an important problem in malignancy. It may be due to chronic causes like malnutrition, marrow infiltration, associated renal or endocrine disorders and it may be complicated with blood loss. Measures like blood transfusion, erythropoietin injections often pose a logistical problem. Parenteral iron injections have proved to be useful in fighting anaemia in some chronic conditions e.g. patients on hemodialysis. *Aims and Objectives:* Primarily to see the observable change in hemoglobin (Hb) level with ferric carboxymaltose (FCM) in treating patients of malignancy on anti-cancer treatment. *Materials and Methods*: Twenty seven patients were enrolled for this study who were suffering from various malignancies. The baseline Hb level was estimated and FCM injection was administered as per the schedule of 500 mg intravenously (IV) weekly once. The overall results of increase in Hb level was noted during the middle of the treatment (chemotherapy or radiotherapy) and later 3-4 weeks after treatment completion. The results were analysed using SPSS and the mean values of initial Hb and after treatment were analysed. Level of significance (p value) was noted using t test. *Results*: In 27 patients the mean initial Hb level was 8.09 g/dl before treatment which increased to 10.28 g/dl after FCM treatment ($p < 0.0001$). *Conclusion*: Treatment with FCM definitely led to a significant increase in Hb level in patients of malignancy undergoing treatment. However, further detailed study is needed to establish its definite role in improving the body iron parameters.

Keywords

anaemia, malignancy, ferric carboxymaltose

Introduction

Anaemia is a pertinent problem in malignancy. Majority of the patients suffer from anaemia either due to the malignant process itself and /or due to blood loss like bleeding per vagina in cervical carcinoma, haematemesis in carcinoma stomach and oesophagus, bleeding per rectum in colorectal carcinoma. Myelosuppression is a definite problem in haematolymphoid malignancies, in metastasis to marrow or even during treatment like chemotherapy and radiotherapy. Moreover in cancer patients apart from all these, factors like poor oral intake, worm infestation and other chronic co-existing illness like tuberculosis often makes the cause of anemia manifold.

Whatsoever is the cause of anaemia in these patients, the definition of anaemia - i.e. a quantitative and /or qualitative loss of Hb for the particular age and sex of the individual - still holds its importance in finding an objective to treat the cause of anemia in cancer patients.

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Measures like whole blood cells /packed red blood cells (PRBCs) transfusion is often used to treat anemia in malignancy. Often recombinant human erythropoietin (rHuEPO) injection is also given subcutaneously (SC) either along with blood transfusion or given alone. Iron preparations have been used in conditions like postpartum anaemia and iron deficiency anemia due to poor oral intake etc. Hence apart from blood transfusion and rHuEPO, it is also important to see whether iron supplementation can also find a solution to anaemia in malignancy.

Aims and objective

This study was conducted to find out the increase in hemoglobin level as the primary end point after administering FCM.

Materials and methods

This was a prospective, non-randomized, open-label, single-arm, observational study done at Radiotherapy Department, North Bengal Medical College and Hospital from the time period of May 2013 to October 2013. Total 27 patients suffering from cancer were studied. The selection criteria were as below:

Inclusion criteria

1. Patients diagnosed to be biopsy proven / fine needle aspiration cytology (FNAC) proven carcinoma.
2. Any cancer and any stage were included.
3. Patients with minimum (min) pre-treatment Hb level of 5.0 g/dl were included

Exclusion criteria

1. Patients who had double primary synchronous or metachronous cancers
2. Patients suffering from any other co-existing disease like tuberculosis, diabetes mellitus, helminthic or parasitic infection, thalassaemia
3. Pre-treatment Hb level below 5 g/dl and above 10 g/dl
4. Any cause of traumatic / operative blood loss
5. Any relapse/ recurrent cancer case who was previously treated by radiotherapy/ chemotherapy or surgery
6. Any history of previous or simultaneous whole blood / PRBCs and erythropoietin injection

All patients were first evaluated as per the diagnosis of biopsy / FNAC proven carcinoma, by initial Hb, total leucocyte count (TLC), differential count (DC), platelets, blood urea, serum creatinine, random blood sugar, liver function tests (LFT) and Hb electrophoresis (in select cases). Hb, TLC, DC and platelets were evaluated weekly during ongoing radiotherapy (RT) and chemotherapy and also examined after 3 weeks of completion of treatment. Radiological examination included chest x-ray, ultrasound of whole abdomen in all cases and contrast enhanced Computed Tomography (CT) scan as per region of interest in select cases (e.g. like CT of abdomen in colorectal cancers). Bone marrow examination was done in haematolymphoid cases only e.g. in lymphoma, chronic myeloid leukaemia (CML). No serum/ bone marrow iron studies were done.

FCM injection was administered to all cases. Dose given was 500 mg every time, dissolved in 250 ml normal saline and administered intravenously over 30 minutes. This was given as per schedule in **Table 1**.

After administering each dose of FCM injection Hb, TLC, DC and platelets were examined at 1 week. The pre-

Table 1
Schedule of FCM administration

Pre-treatment and interim Hb (g/dl)	FCM administration	At intervals of
9 - 10	once	—
7 - 8.9	twice	1 week
6 - 6.9	thrice	1 week
5 - 5.9	4 times	1 week

treatment (pre t/t) Hb level and also the interim Hb level were considered to decide the number of times FCM injection needs to be given. On account of chemotherapy induced leucopenia/neutropenia and thrombocytopenia G-CSF injection and platelet transfusion were given accordingly. No oral haematinic supplementation was allowed.

The statistical analysis was done taking into consideration the Hb level of the patient before initiation of any surgery/ chemotherapy/radiotherapy and 3 weeks after completion of the entire treatment. Oral hormonal therapy or oral chemotherapy was not taken as an end point. For patients on an oral antineoplastic therapy the Hb level at end of 1 month after initiation of the oral therapy was taken into consideration as the post-treatment (post t/t) Hb level. Statistical analysis was done by measuring mean [± standard deviation (SD)] of the Hb level of both pre and post treatment. Paired 't' test and p values were calculated for pre and post-treatment Hb level using SPSS software version 19.

Results

Total 27 patients were evaluated. The mean pre-treatment Hb level was 8.09 (± 1.0) and mean post-treatment Hb level was 10.28 (± 1.23) and a comparative line diagram (**Fig. 1**) depicts the differences in Hb level before and after giving FCM. The X axis shows the no of patients and the Y axis shows the Hb level in g/dl. The p value of the paired t test (of the mean Hb level) before and after treatment was significant (p <0.0001) (**Table 2, Fig. 1**)

The 27 patients were further analysed as per their type of cancer. **Fig. 2** shows number of patients in various subgroups. They were classified as suffering from carcinoma cervix (Ca Cx) [n=7]; Ca breast [n= 7]; haematolymphoid malignancy (lymphoma, leukaemia) [n=3]; head & neck Cancer (H & N Ca) [n=3]; colorectal Ca [n=4] including 1 patient of anal canal carcinoma; Ca stomach [n=1] and Ca lung [n=2]. Further analysis was done based on 5 major types - Ca Cx, Ca Breast, H & N Ca), Colorectal Ca and Haematolymphoid malignancies.

Fig. 1

Comparative line diagram between the pre-treatment, interim and post-treatment Hb level
x-axis - no of patients
y-axis level of Hb in g/dl

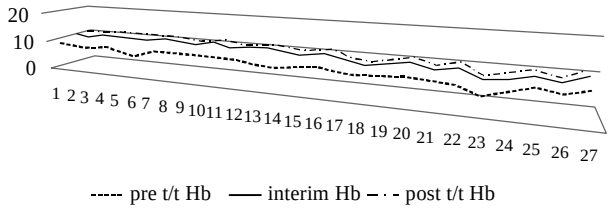
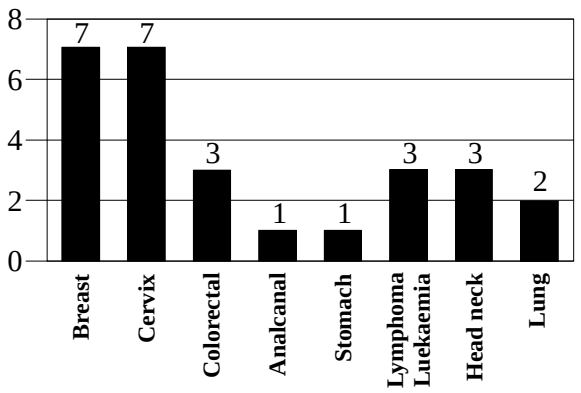


Fig. 2

No of patients in each type of cancer



The mean values of pre t/t and post t/t Hb in Ca Cx, Ca breast, H & N Ca, colorectal Ca and Haematolymphoid malignancies were evaluated and comparison of change in Hb (pre versus post t/t Hb) was done using paired 't' test to find out the level of significance if any. Results of the same are given in **Table 3**.

Table 2
Change in Hb pre and post FCM treatment

	n	Pre-t/t Hb	Post-t/t Hb	p
Overall patients	27	8.09 ± 1.0	10.28 ± 1.23	<0.0001

Table 3
Subgroup analysis as per type of cancer Change in Hb pre and post FCM treatment

Patients with	n	Pre-t/t Hb	Post-t/t Hb	p
Ca cervix	7	7.20 ± 1.19	10.06 ± 1.74	0.001
Breast Ca	7	8.84 ± 0.40	10.7 ± 0.62	0.000
H & N Ca	3	8.87 ± 0.45	11.13 ± 0.59	0.010
Colorectal Ca	4	7.68 ± 0.86	9.65 ± 1.59	0.174
Haematolymphoid malignancy	3	7.93 ± 0.51	10.17 ± 1.15	0.107

Pre-t/t: Pre-treatment; Post-t/t: Post treatment

Fig. 3
Comparison of pre- and post-treatment mean Hb level in each subgroup

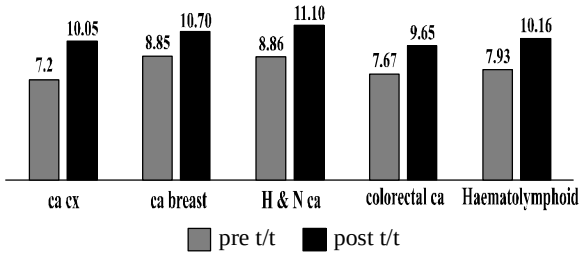


Fig. 3 depicts the differences in Hb pre and post t/t in each subgroup.

Discussion

Anaemia is a very important problem in malignancy. The release of cytokines like interleukin -1 (IL-1) and interferon - γ (IFN- γ) suppress the erythropoietin (EPO) production and along with this hepcidin[1], which is made in liver, is also increased and it suppresses iron absorption. The overall result is a chronic hypoproliferative state. However, in cancer patients anaemia is often a result of a combination of multiple factors- like poor nutritional state, post-surgical state, blood loss, associated renal disease, endocrine disorder, inflammation or ineffective erythropoiesis due to marrow infiltration and treatment induced e.g. chemotherapy and radiotherapy. Hence there is both a problem of acute conditions like blood loss anaemia and chemotherapy/ radiotherapy induced acute myelosuppression apart from the chronic malignant disease process and other associated factors leading to anaemia. Hence the measures taken to overcome this complex situation have to be very wisely planned encompassing both the chronic hypoproliferative state and acute problems if any. This is unique to anaemia of malignancy unlike other conditions leading to anaemia where only a single aspect like renal, endocrine or nutrition is of concern.

Acute conditions like blood loss or treatment induced acute myelosuppression are often tackled with blood transfusion depending on the severity of the condition. However, often the patients face problems related to desired blood group availability, logistical problems of bed availability for blood transfusion and transfusion related hypersensitivity reactions. Sometimes this leads to interruption of the treatment of cancer thus leading to an inadequate response and ultimately treatment failures.

In medical practice, chemotherapy-induced anaemia is frequently also treated with erythropoiesis-stimulating agents (ESAs) and/or blood transfusions. However, many patients do not respond to ESA treatment and blood transfusions with aggressive ESA treatment may increase mortality[2-7]. Therefore, anaemia treatment guidelines aim to prevent transfusions and to minimize ESA dosages[8-10].

In an asymptomatic patient with established iron deficiency anaemia, oral iron therapy is adequate. Typically 300 mg of elemental iron per day is given orally and it results in absorption up to 50 mg/day. However a sustained oral iron therapy for 6-12 months is necessary to correct the iron deficiency and it may be associated with abdominal pain, nausea, vomiting or constipation in 15-20% patients. In patients suffering from lymphoma and gastrointestinal cancers, these associated complications often make matters worse[11-12].

Parenteral iron therapy is an important solution to the above problems and is often used based on formula-

Amount of iron required (in mg) = Body weight (kg) × 2.3 × [15 - patient's Hb (g/dl)] + 500

Iron dextran was previously used as a parenteral form but serious adverse reactions of anaphylaxis limit its use. Iron gluconate and iron sucrose were developed and used and they overcome the problems of iron dextran.

FCM is a new generation IV iron formulation which is a macromolecular ferric carbohydrate complex, that allows controlled delivery of iron within the cells of the reticuloendothelial system and deliver it to iron binding proteins like ferritin and transferrin with minimum risk of release of large amount of ionic iron in the serum. Hence it is associated with a minimal risk of anaphylaxis and other side effects. Intravenously a dose of 1000 mg can be given within 15 minutes and the total iron concentration can be increased in a dose dependent manner. It is distributed primarily to the marrow and repeated weekly administration does not result in accumulation of transferrin iron[13-14].

In several randomized, multicentric clinical trials IV FCM was effective in the treatment of various patient populations like post-partum anaemia, inflammatory bowel disease, heavy uterine bleeding, and chronic kidney disease with or without hemodialysis. Taking into consideration these results the role of FCM in treating and fighting anaemia in malignancy has been explored.

Recently Steinmetz *et al*., from Germany[15] has published the first dataset that documents the effectiveness and excellent tolerability of FCM in cancer patients. Of 639 patients enrolled in 68 haematology/oncology practices in Germany, 619 received FCM. The median total iron dose was 1000 mg per patient (interquartile range 600–1500 mg). The median Hb increase was comparable in patients receiving FCM alone (1.4 g/dl [0.2–2.3 g/dl; N = 233]) or FCM + ESA (1.6 g/dl [0.7–2.4 g/dl; N = 46]). Patients with baseline Hb up to 11.0 g/dl and serum ferritin up to 500 ng/ml beneûted from FCM treatment (stable Hb ≥ 11.0 g/dl). The substantial Hb increase and stabilization at 11–12 g/dl in FCM-treated patients suggest a role for this IV iron alone in anaemia correction in cancer patients.

Considering these results, present study was undertaken as an observational study to notice the response to FCM and its tolerability amongst cancer patients on treatment in an Indian rural medical college hospital with limited resources. Out of 27 patients, 7 patients were of cervical cancer who had problems of blood loss anaemia along with hypoproliferative and nutritional anaemia. The mean Hb level of cervical cancer patients was 7.2 g/dl and with FCM treatment it increased to 10.06 g/dl (p = 0.001). Similar results were observed with FCM treatment in 7 patients of breast cancer who had to undergo surgery, extensive myelosuppresive chemotherapy and thoracic radiotherapy. The pre-treatment mean Hb level in these patients was 8.84 g/dl which increased to 10.7 g/dl post FCM treatment. Bleeding was also a problem in 4 patients of colorectal cancer. FCM treatment did improve the Hb level in these patients as well (mean pre t/t Hb= 7.68 g/dl and mean post t/t Hb = 9.65 g/dl), but the results were not significant (p=0.174). Patients of H & N cancer study also showed a significant improvement in mean Hb level (**Fig. 3, Table 3**). Marrow infiltration was a very important factor in patients of lymphoma (NHL) and leukaemia (CML). FCM treatment had a good response in maintaining the Hb level in NHL and CML patients. Overall, the mean Hb increase was from 8.09 to 10.28 g/dl in these 27 patients (p <0.0001).

This was a non-randomized, single arm, observational study. Owing to limited resources in our rural medical college hospital the serum ferritin, transferrin and other indices like total iron binding capacity (TIBC) could not be done. These were the major limitations of the study.

Conclusions

This is the first study in India to study the effect of FCM in treating anaemia in malignancy amidst a lot of logistical constraints. In this respect a further more detailed randomized double arm study taking into account a control arm with more number of patients and over a more prolonged time period may surely help in understanding the role of FCM in battling anaemia of malignancy. The major question still remains whether parenteral iron will be able to overcome the need for blood transfusion in mild to moderate anaemia while treating cancer patients.

Acknowledgment

The brand of FCM injection used in this study was Orofer-FCM from Emcure Pharmaceuticals Ltd.

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