Original Article

Indian Journal of Cancer Education and Research
Volume 11 Number 2, July - December 2023
DOI: http://dx.doi.org/10.21088/ijcer.2321.9815.11223.1

Real World Study to assess Efficacy of Ferric Carboxymaltose in Treatment of Anemia in Solid Tumors in India (REAL-FCM Study)

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How to cite this article:
Joydeep Ghosh, Rakul Nambiar, Boben Thomas *et al.*/Real World Study to assess Efficacy of Ferric Carboxymaltose in Treatment of Anemia in Solid Tumors in India (REAL-FCM Study)/Indian J Canc Educ Res 2023;11(2):61-65.

Abstract

Objectives: Cancer related anemia is common comorbid treatable condition with potential impact on treatment response and quality of life. Data on treatment with ferric carboxymaltose (FCM) an i.v. iron preparation in cancer related anemia due to iron deficiency in Indian patients is sparse.

Materials and Methods: In this retrospective medical record based study, data of 147 patients with solid organ malignancies and iron deficiency anemia (IDA) who received FCM were retrieved. Hematological parameters *i.e.* hemoglobin (Hb), serum ferritin and transferrin saturation (TSAT) were analyzed at baseline (*i.e.* before FCM administration) and at 4 weeks. Serious adverse events which were recorded in source documents on day of FCM infusion were collected.

Results: At the baseline, mean Hb was 8.7±1.2 gm/dl. At end of 4 weeks there was a statistically significant improvement in the mean Hb level of 9.79±0.87 (p value <0.001). The mean serum ferritin and serum TSAT level also showed a significant improvement (p value for both < 0.001). No SAE were recorded on day of FCM administration.

Conclusions: This study adds to the wealth of Indian evidence of efficacy of FCM in cancer related anemia due to iron deficiency, as already demonstrated in other published studies. FCM may be considered as preferred i.v. iron preparation in this setting.

Keywords: Cancer related Anemia; Real world study; Ferric carboxymaltose; Intravenous iron; Retrospective.

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Received on: 03.04.2023

Accepted on: 31.05.2023

INTRODUCTION

Cancer related anemia is not an uncommon condition in patients presenting with solid tumor malignancies. It has potential impact on quality of life, response rates to treatment and even overall survival.[1,2] Recognizing this condition and treatment

is essential. Cancer related anemia as defined by NCCN and ESMO guidelines is hemoglobin less than 11 gm/dl or ≥2 g/dL below baseline in patient with cancer.[3,4] Evaluation of causes involves blood investigations for iron studies, vitamin B12/folate deficiency, assessment of blood loss.[5] Preexisting malnutrition is important cause of baseline anemia in India.[5]

Blood transfusion and erythropoiesis stimulating agents (ESA) in appropriately selected patients can significantly improve hemoglobin (Hb) levels, decrease transfusion requirements, and improve QOL.[6,7] Iron correction is important component of anemia treatment with exclusion of other causes. In patients with cancer related anemia, both absolute and functional iron deficiency can occur. Intravenous treatment with iron may be offered in both settings.[6] Ferric carboxymaltose (FCM), a non-dextranparentral iron preparation is well studies in anemia of nonmalignant conditions *i.e.* chronic renal disease[8] and gynecology.[9] There is lack of Indian data on efficacy of i.v. Ferric Carboxymaltose in cancer related anemia, hence there is need to generate real world data of patients treated with this iron preparation.

This study aims to generate real world Indian data on efficacy of FCM in treatment of iron deficiency anemia associated with solid organ malignancies.

MATERIALS AND METHODS

This a retrospective study. Medical records (electronic or paper based) from May 2021 to April 2022 were retrieved from 3 sites across India in a uniform format. Patients with solid organ malignancies with Hb less than 11 gm/dl treated with i.v. iron FCM 1000 mg single dose (Encicarb1K, Emcure Pharmaceutical Ltd, Pune) were included in the study. Patients who have received any other i.v. iron other than Ferric Carboxymaltose or on oral iron in previous 4 weeks were excluded. Data was collected at 2 time points, baseline (*i.e.* before FCM administration) and 4 weeks or later post FCM. Patient demographics, cancer diagnosis, anti-cancer treatment and iron studies parameters (hemoglobin, Serum ferritin, TSAT) at baseline and after 4 weeks or later were collected. No follow up was done to retrieve any missing data and only those patients who had minimum Hb data at both time points *i.e.* at baseline and 4 weeks or any time later after FCM administration was considered for data entry. Mild, moderate and severe anemia was defined as 10-11 gm/dl, 8- 9.9gm/dl and< 7.9 gm/dl respectively as per ESMO reference ranges. Study aimed to collect data from at least 100 patients to derive meaningful outcomes in primary outcomes. No formal statistical analysis was made to derive on sample size. Descriptive Statistics was used to analyze the data. Only those serious adverse event (SAE) which are specifically recorded due to FCM administration as per source documenton day of FCM administration were collected. Primary outcome of the study was to evaluate change in the Hemoglobin after 4 weeks or next earliest follow up visit post one infusion of FCM 1000mg in patients with cancer associated anemia. Secondary outcome was to evaluate change in parameters of iron status (TSAT and serum ferritin).

RESULTS

Data of 147 patients who at least had 2 recordings of Hb (*i.e.* baseline and 4 or weeks or later) were collected. All patients had received Encicarb 1000 mg single dose as part of their routine care of treatment of anemia at discretion of evaluation of treating physician. Mean age of the patients was 54.7 years. All patients had locally advanced or metastatic disease. 75 % (n = 110) of the patients were females. 13% (n=19), 67% (n=99), 20% (n= 29) of patients had mild, moderate and severe anemia respectively. Most patients had breast cancer 33% (n = 49) followed by lung cancer 16% (n = 24). (Table 2) Paclitaxel based chemotherapy was received by 54% (n=79) and platinum based chemotherapy by 35% (n=52).

At the baseline, mean Hb was 8.7±1.2gm/dl. After 4 weeks or later of FCM administration, there was 1.08 gm/dl/dl improvement in the cohort to mean Hb level of 9.79±0.87 which was statistically significant (p value <0.001). The mean serum ferritin improved by 38 ng/ml from the baseline (p value <0.001) and serum TSAT% improved from mean value of 17% from baseline to 41% (p value < 0.001).(table 1).

Adverse event reporting in this study was based on availability of already existing records as per source documents. No serious adverse events were recorded in the study.

DISCUSSION

This real world retrospective study demonstrates a statistically and clinically significant increase in hematological parameters post FCM administration in patients with solid organ cancer and anemia. This increase was evident at 4th week of iron

Table 1: Efficacy of Ferric Carboxymaltose in terms of Change in Hemoglobin, Serum ferritin and Transferrin Saturation (TSAT)

Hematological Parameters		N	Mean ± SD	Mean difference ± SD	P Value
Hemoglobin (gm/dl)	Baseline	n = 147	8.7±1.2	-1.08±1.21	<0.001
	4 weeks		9.79±0.87		
Serum. Ferritin (ng/mL)	Baseline	n=45	16.38±8.53	-38.95±45.89	<0.001
	4 weeks		55.33±45.53		
TSAT (%)	Baseline	n =50	17.1±6.72	-24.09±10.66	<0.001
	4 weeks		41.19±11.38		

Table 2: Solid tumor profile included in the study

	Number of patients (n)
Lung	24
Breast	49
Cervix	7
Colon	4
GI/GU	22
Others	41

administration which in line with similar studies where increase was shown since 3rd week.[10]

Correcting of anemia has proven benefits to improve quality of life and survival benefits in cancer related anemia.[2] The prevalence of anemia in varies as per stage and tumor type. Pandey *et al*[11] reported 61% prevalence of anemia in single center study in Northeast India while John *et al*[12] reported prevalence of 52% in South India. Sharma *et al*[13] reported baseline prevalence of 46.5% in patients with breast cancer. Baseline anemia is more common in females during to nutritional factors. In our study, females had greater proportion of anemia than males *i.e.* 75% which was higher reported compared to other Indian studies which reported 42-45%[11,14] but compared to an another study which reported around 80%.[10]

Higher incidence of anemia is reported amongst breast and lung cancer in literature.[15,16] In this study, same results are reciprocated in these two cancer types. Majority of the patients in this data had moderate to severe anemia (87%). This may be again attributed to existing malnutrition, cancer cachexia and higher female population in this study who had existing anemia.38 [11,14] to 45%[12] of the patients diagnosed with cancer and anemia had moderate to severe anemia at presentation in various Indian studies.

Majority of the patients were on platinum or paclitaxel based chemotherapy. Since the study didn't capture the chemotherapy regime and cycle, we were unable to correlate if chemotherapy was contributory factor for decrease in hemoglobin. Chemotherapy induced anemia is well known and meta-analysis of i.v. iron in this condition is proven to demonstrate improvement in hematopoietic response and blood transfusion need.[17]

The study demonstrated 1.08 gm/dl hemoglobin increase in this cohort of patients with various solid tumors which is 12% increase over the baseline. Corresponding to increase in hemoglobin, i.v. FCM administration parellelly increased serum ferritin and TSAT. In a similar prospective study[10] in patients with cancer related anemia in solid tumors, 1.46 gm/dl increase after administration of FCM was observed although median FCM dose was higher in that study. Calleja *et al*[18] demonstrated 1.5 gmdl increase in hemoglobin over control group in patients with colon cancer anemic patients undergoing elective surgery with curative intention. Data from Germany[19] in patients with both solid tumors and hematology demonstrated 1.4 gm/dl increase post 1000 mg FCM.

No serious adverse event were recorded in the study which confirms that infusion on day of administration was well tolerated. This interpretation may be confounded by limited availability of data because of retrospective nature of study and possibility of SAE's not being well documented in source documents.

Our study has some limitations. Because of retrospective nature of the study, we could analyze limited data points. While it was mandatory to have 2 recordings of hemoglobin pre and post FCM infusion, serum ferritin and TSAT were available in only ~34% of the records. This may demonstrate real world practice of physicians to rely on hemoglobin as only deciding parameter and limit study analysis for efficacy in absolute and functional IDA. NCCN recommends treatment of IDA related to cancer based on Hb, ferritin and TSAT status.[4] Secondly because of cross sectional nature of study, we could retrieve last chemotherapy details but not number of previous cycle and its correlation with anemia. Hence we are unable to interpret if anemia is due to chemotherapy cycle, existing nutritional

deficiency or cancer cachexia. Nevertheless, FCM was associated with increase in Hb in entire cohort of patients.

To best of our knowledge this is first data in Indian patients to demonstrate efficacy of FCM in cancer related anemia in solid tumors in sizable sample of patients. Study in Indian patients from an Oncology and Hematology clinic[20] in 77 patients have demonstrated mean Hb increase of 4.2 gm/dl at 3 weeks although that study was not specific to solid tumors. Efficacy of FCM in Indian patients in other indications like iron deficiency anemia in gynecologic indications is also very well established.[21]

Iron studies at baseline should be part of evaluation of every cancer patient with anemia and patient categorized to absolute vs functional iron deficiency for optimal guideline recommended treatment strategies. Intravenous iron has been proven to have better response than oral iron in improving hematological parameters, hence should be considered over oral iron avoiding GI tolerability issue.[17]

CONCLUSION

Real world Indian evidence on use of FCM 1000 mg in anemia in cancer patients is established in this study which adds to wealth of efficacy of evidence of FCM as already established in other non-cancer indications. Further studies should evaluate other parameters like quality of life, survival which was prohibitive in this retrospective design.

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