Official title:

The use of intravenous ferric carboxymaltose (FCM) without erythropoiesis-stimulating agents (ESA) in the treatment of anemia in cancer patients undergoing chemotherapy with or without radiotherapy

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The Study Will Be Conducted According To The Ethical Principles That Have Their Origin In The Declaration Of Helsinki, The Best Practices Described In The ICH E6 Guidance On Good Clinical Practice And The Local Laws Of Jordan

Title	The use of intravenous ferric carboxymaltose (FCM) without erythropoiesis-stimulating agents (ESA) in the treatment of anemia in cancer patients undergoing chemotherapy with or without radiotherapy
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Protocol Content

1. Investigator Statement

1. The INVESTIGATOR shall be responsible for all the acts of the sub-investigator(s) and any party designated by the Investigator to fulfill the Investigator's obligations under this PROTOCOL.

2. The INVESTIGATOR shall procure that sub-investigator(s) and any party designated by the Investigator complies with all regulatory requirements and mandates for the conduct of clinical trials.

3. The INVESTIGATOR will assure that sub-investigator(s) and any party designated by the Investigator to support the conduct of this trial will be qualified and have attended the required training planned for this trial.

4. The INVESTIGATOR shall protect the rights and welfare of patients participating in the CLINICAL TRIAL in accordance with the PROTOCOL.

5. The INVESTIGATOR shall obtain and maintain any and all licenses, permits, approvals, and patient informed consent documents required by the Protocol and Regulations for conducting of the relevant part of the Clinical Trial from the INSTITUTION, IRB/EC and/or any other authorized body. Specifically, INVESTIGATOR shall obtain a signed and legally valid written Informed Consent Form from each potential participant in the Clinical Trial (or his/her legal guardian, as appropriate) before initiating any procedures specified in the Protocol.

I have revised this version of the protocol and agree to conduct the trial in accordance with all the requirement set in the protocol, the applicable laws and regulations and in accordance with the ethical principles outlined in the declaration of Helsinki.

_____

Principal Investigator Name, Signature & Date

2. Clinical Trials Unit Role & Responsibility

The clinical trials unit primary job is to support the execution and conduct of clinical trials at KHCC. Such support includes but is not limited to the development of trial related documents. Such documents used include the source template for this clinical trial protocol which may not necessarily be fully completed by the unit in response to a request from the investigator. The investigator may have elected to complete his protocol by himself.

The involvement of the clinical trial unit is generally arranged with the Principal Investigator and defined for any of its employees in the delegation sheet set for the trial. Such arrangements are finalized during an initiation meeting planned for the trial before the first patient is recruited. Tasks that will be carried for this protocol:

1. Assistance with protocol development
2. Assistance with the development of the study CRFS and ICFs
3. Training the trial team on the study protocol
4. Development of the trial master file
5. Coordination with the biostatistics unit and data management unit support
6. Following –up on the study conduct with the investigator.
7. Assist investigator in completing the trial master file and archiving of the trial for the planned period of retention.
8. Registration of the Trial to a public registry if required (clinicaltrial.gov)

_____

Clinical Trial Unit Head Signature

3. List of Abbreviations

AE	Adverse Event
AID	Absolute Iron Deficiency
CAA	Cancer Associated Anemia
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
CRP	C-Reactive Protein
ECOG	Eastern Cooperative Oncology Group
ESA	Erythropoiesis-Stimulating Agents
FCM	Ferric Carboxymaltose
FID	Functional Iron Deficiency
Hb	Hemoglobin
ICH	International Conference on Harmonization
IDA	Iron Deficiency Anemia
IRB	Institutional Review Board
JFDA	Jordan Food and Drug Administration
KHCC	King Hussein Cancer Center
QOL	Quality of Life
Rx History	Drug History
SAE	Serious Adverse Event
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
US FDA	the United States Food and Drug Administration
WMA	World Medical Association

4. Summary:

<table>
<tr><td>PROTOCOL TITLE</td><td>The use of intravenous ferric carboxymaltose (FCM) without erythropoiesis-stimulating agents (ESA) in the treatment of anemia in cancer patients undergoing chemotherapy with or without radiotherapy</td></tr>
<tr><td>STUDY OBJECTIVES</td><td>The study aims to investigate the effect of FCM (without ESAs) on anemic cancer patients undergoing chemotherapy (with or without radiotherapy); stratified by status of iron deficiency (i.e. non-iron deficient vs. iron deficient patients). The study will also try to find out whether serum level of Hepcidin and CRP can correlate with response.</td></tr>
<tr><td>STUDY ENDPOINTS</td><td>Primary Endpoint:
Response Rate: Percentage of patients with Hb increment of at least 1.0 gm/dL.
Proportion of patients achieving correction of anemia (Hb >11.0 gm/dL)
The mean Hb change from baseline to week 12
Secondary Endpoints:
Response in relation to Hepcidin level.
Response in relation to CRP level.
Response in relation to base line iron deficiency status; iron-deficient or not.
Parentage of patients who will require blood transfusion or ESA treatment</td></tr>
<tr><td>STUDY DESIGN</td><td>This study is a nonrandomized, single arm, open-label study stratified by iron-deficiency status.
Patients will receive one or two doses of FCM, based on the body weight and Hb level. Patients will be followed-up for a total of twelve weeks. The study is divided into a screening, treatment and follow-up phases and is expected to be completed in 12 months.</td></tr>
<tr><td>INVESTIGATIONAL PRODUCT</td><td>Ferrous Carboxymaltose (Ferrinject®) 1000 mg/20 ml
The dose will be based on the following regimen:
<table><tr><td rowspan="2">Baseline Hb (g/dL)</td><td colspan="2">Body Weight (Kg)</td></tr><tr><td><70</td><td>>70</td></tr><tr><td><10</td><td>1500 mg</td><td>2000 mg</td></tr><tr><td>≥10</td><td>1000 mg</td><td>1500 mg</td></tr></table></td></tr>
<tr><td>STUDY POPULATION</td><td>One hundred (100) anemic cancer patients undergoing chemotherapy (with or without radiotherapy) identified as eligible per selection criteria of the study will be enrolled.
A patient is considered eligible if he meets all the inclusion criteria and none of the exclusion criteria.</td></tr>
</table>

INCLUSION CRITERIA	▪ Patient is an adult ≥ 18 years old at the time of informed consent. ▪ Patient has pathologic diagnosis of solid tumor (breast cancer, colorectal, lung, sarcoma, head & neck, sarcoma, genitourinary or gynecological cancer). ▪ Patients who started chemotherapy (with or without radiotherapy) or planned to receive chemotherapy for at least 12 weeks. ▪ Patient has an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2. ▪ Patient with Hb ≤11 g/dL. ▪ Patient has a Life expectancy at least 6 months. ▪ Adequate hepatic & renal function defined as a serum aspartate aminotransferase or alanine aminotransferase level that are no more than 3 times the upper limit of the normal range, a serum bilirubin level that is no more than 2 times the upper limit of the normal range and a serum Creatinine level of less than 2 mg per deciliter. ▪ Patient is able to understand and provide informed consent to participate in the study.
EXCLUSION CRITERIA	▪ Patient has Hb ≤ 8.0 g/dL ▪ Patient presenting with hematologic malignancy including any of the following: Acute Leukemia, MDS (Myelodysplastic Syndromes), CML, CLL, Multiple Myeloma, Myelodysplastic syndrome and lymphoma with bone marrow involvement ▪ Prior gastric surgery. ▪ Patients on definitive radiotherapy alone. ▪ Patients with relevant history (within six weeks) or clinical evidence of hemolysis or active bleeding that could, in the investigator's judgment, be a potential cause for the anemia (no gross hematuria, hemoptysis, hematochezia or melena and negative stool for hemoccult-at least one reading) ▪ Presence of other nutritional anemia; deficiency of vitamin B12<187pg/ml and deficiency of Folate<3.1ng/ml according to the local laboratory normal ranges. ▪ Patient has Iron overload (Serum Ferritin > 800 ng/ml or Transferrin saturation (TSAT) > 40%) ▪ Patient is pregnant or lactating. ▪ Patient has a personal or family history of hemochromatosis. ▪ Patient has hypersensitivity to any form of IV iron. ▪ Patient has received red blood cells (RBCs) transfusion or used erythropoietin within 2 weeks of enrollment into the study. ▪ Patient has received any form of IV iron within the last 12 weeks ▪ Patient has received oral iron supplements within 1 month of enrollment to the study, except for multivitamin supplements containing less than 30mg iron.
EFFICACY ASSESSMENTS	▪ Hb at baseline and at 3,6,9 and 12 weeks

SAFETY ASSESSMENTS	▪ Serum ferritin level (baseline and at 12 weeks) ▪ Liver Enzymes (ALT, AST), Alk Phosphatase, GGT, LDH and serum phosphate levels at base line and at week-3 ▪ Record all adverse events
OTHER ASSESSMENTS	▪ CRP levels at baseline ▪ Hepcidin at baseline
STUDY SITE	King Hussein Cancer Center (KHCC)
ETHICAL CONSIDERATIONS	▪ The study will be submitted for ethical review and approval before execution. ▪ Informed consent will be obtained from study patients before implementing any study procedure.
STATISTICAL PLAN	Descriptive statistics will be used to present the two groups baseline characteristics and disease information. Analysis will be done for the two groups separately: o **Group I**: Patient Iron-deficiency anemia based on iron studies at base line o **Group II**: Patient with non-iron deficiency anemia • Hb test results will be presented as mean, median and range through all twelve weeks. • Average percent change from baseline will be used to show the changes of Hb level. Comparison between means of Hb level will be made between the baseline Hb and Hb levels in the following weeks using Paired T-test. • Response to IV iron therapy will be assessed in relation to Hepcidin and CRP levels. • Univariate analysis will be used to assess the effect of patient characteristics and disease variables on the response using Chi square test or fisher's exact test. • Adjusting for all significant factors that may affect the response will be done using Logistic regression. • Odds ratio out of the Logistic regression will be reported with their corresponding 95% CI. • A significance criterion of $p< 0.05$ will be used in the analysis. All analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

5. Introduction

5.1 Background

Anemia, defined as an inadequate circulating level of hemoglobin, is a common complication of cancer and its treatment; especially in patients undergoing chemotherapy and/or radiotherapy. It may arise from the underlying disease, bleeding, poor nutrition, chemotherapy, or radiation therapy. Prevalence of anemia varies between 30 and 60 %. Preliminary studies suggest that survival and loco-regional control after radiation therapy, especially in head and neck and cervical cancers, may be compromised by anemia.[1,2]

Anemia often worsens symptoms such as fatigue, weakness, and dyspnea, and thus may have a negative impact on the quality of life (QOL) and performance status of patients with cancer. Thus, to improve physical functioning, QOL, and prognosis in patients with cancer, it would be reasonable to take a proactive approach in identifying populations who need treatment for cancer-associated anemia (CAA) and provide a timely management.[3,4,5,6]

5.1.1 Transfusions

Blood transfusion is an effective way to replace depleted Hb within a short period, but the effect is, unfortunately, temporary and can cause serious adverse risks and increase mortality[7].

5.1.2 Erythropoiesis-stimulating agents (ESAs)

ESAs were proposed as an effective treatment for anemia for several years. Randomized clinical trials in patients with CAA has demonstrated that ESAs produced significant increases in Hb level, decreased transfusion requirements, and improved QOL[8,9,10,11,12,13]. However, 30%-50% of patients do not respond to such agents. Lack of response to erythropoietin stimulation in patients with cancer is partly attributed to the functional iron deficiency state, in which the high rate of erythropoiesis exceeds the delivery of usable iron, despite adequate iron stores. Many randomized trials were conducted to examine the role of IV iron in addition to ESAs in the treatment of anemia in patients with cancer[14,15,16,17]. Many of these studies showed improvement in ESA response, time to maximal response, reduction in ESA dose, and improvement in QOL parameters, when measured, in favor of the combination over ESAs alone. The observed benefit was independent of baseline iron parameters.

Several recent studies had raised serious concerns related to shortened overall survival, or time to tumor progression in patients treated with ESAs especially among patients whose Hb reached levels

beyond 12 g/dL. These concerns, in addition to higher incidence of thromboembolism, resulted in a significant decline in the use of these agents especially among potentially curable cancers[18,19,20,21]. In 2008, Centers for Medicare and Medicaid Services recommended through new guidelines that ESAs are not to be used in patients with long life expectancy.

5.1.3 Parenteral Iron

Iron plays an important role in hemoglobin synthesis and an inadequate supply is a major element in the pathogenesis of anemia. Intravenous iron therapy is routinely used to treat iron-deficiency anemia especially so in patients with severe anemia and in those who failed or could not tolerate oral formulations. Absolute iron deficiency (AID) occurs when iron delivery is impaired because iron stores are depleted (serum ferritin < 100 ng/mL; transferrin saturation (TSAT) < 20%).

Functional iron deficiency (FID), on the other hand, occurs when access to iron stores is restricted or too slow to keep-up with the process of erythropoiesis[22]. In cancer, tumor cells interact with the immune system leading to a chronic state of inflammation. Pro-inflammatory cytokines are released leading also to the release of Hepcidin; a small (25 amino acids) peptide produced by the liver. Hepcidin is a regulator in iron homeostasis. It binds to ferroportin-expressing cells, inhibiting iron transport across cell membranes and decreasing accessibility to the iron stores. At high enough circulating levels, it impairs gastrointestinal absorption of dietary iron. This state of blocked release from stores and inhibited absorption leads to an increased frequency of iron-restricted erythropoiesis. Hence, it was proposed that patients identified with FID may benefit from the extra doses of iron to overcome the negative effect of Hepcidin[23,24,25,26].

5.2 Aim of Study

In a previous pilot study conducted by our group, we investigated the use of IV iron without ESAs in a group of non-iron deficient anemic cancer patients undergoing chemotherapy. Patients were given 12 weekly short infusions of ferric sucrose while on chemotherapy. The mean increment in hemoglobin level for the 15 patients who completed at least 9 treatments was 1.7 g/dL (median, 1.1 g/dL; range, -1.9 g/dL to 3.2 g/dL). Five (20.0%) patients were transfused and considered as treatment failures. No treatment-related adverse events were reported.

With such results and to move forward with the investigation, we have considered using a new intravenous iron formulation. Ferric carboxymaltose (FCM), is widely used to treat iron deficiency anemia in different clinical settings including pregnancy-related and in chronic renal failure patients.[27].

Therefore, the study aims to investigate the effect of FCM without ESAs on anemic cancer patients undergoing chemotherapy or radiotherapy; stratified by status of iron deficiency (i.e. non-iron deficient vs. iron deficient patients).

Furthermore, we aim to investigate the value of Hepcidin and also CRP (which is closely associated with inflammatory cytokines, as well) as predictors of response.

6. Study Objectives

6.1 Primary objectives:

- Assess the response to FCM in each strata

6.2 Secondary Objectives:

- Assess the utility of hepcidin and CRP in predicting response to FCM
- Assess the effect of FCM on the need for blood transfusions
- Assess the effect of FCM on the need for ESAs

6.3 Study Endpoints

6.3.1 Primary Endpoint:

- Response Rate: Percentage of patients with Hb increment of at least 1.0 gm/dL.
- Proportion of patients achieving correction of anemia (Hb >11.0 gm/dL)
- The mean Hb change from baseline to week 12

6.3.2 Secondary Endpoints:

- Response in relation to Hepcidin level.
- Response in relation to CRP level.
- Response in relation to base line iron deficiency status; iron-deficient or not.
- Parentage of patients who will require blood transfusion or ESA treatment

7. Rationale

Unresolved anemia is a problem in cancer patients. If it remains uncorrected, it will negatively impact patient response to treatment and QOL. With the limitations set on use of ESAs in cancer and absence of alternatives that lower the need for transfusion, iron loading is a tempting choice to explore. Trials on the use of iron as a lone treatment are generally few. This study is important in that it allows assessing FCM in both AID and FID. It will shed light on a different dosing regimen and help build understanding on the use of Hepcidin and CRP as predictors of response.

7.1 Dose Rationale

Ferric carboxymaltose in a single dose, or two, is assumed sufficient to produce a clinically observable change in the status of hemoglobin in 12 weeks' time comparable to what has been achieved with small frequent doses. This has been demonstrated before using FCM in FID and lymphoid malignancies patients. FCM iron complex allows rapid increase in iron levels peaking within approximately an hour. Total serum iron levels then rapidly decline reaching normal levels within 24 to 72 hr after infusion. This allows sufficient amount of time for the body to engage the circulating iron in erythropoiesis and hence induce the proposed response. Though single high FCM dose is expected to be safe and tolerable, dosing of patients will be based on body weight to lower any chances of unwanted risks.

8. Patient Selection

8.1 Source Population and Sample size

The study aims to enroll anemic cancer patients planned to receive chemotherapy or radiotherapy. The study sample will be selected to fulfill the selection criteria. The patient is eligible if he meets all the inclusion criteria and none of the exclusion criteria. The estimated sample size necessary in each strata is 50 which can be easily recruited in 10 months.

8.2 Eligibility Criteria

Evaluation of eligibility is the sole responsibility of the PI and will be documented in the patient CRF. If deviations from selection criteria occur, the PI will provide the proper justifications for continued inclusion of the patient in the study which will be documented in the CRF.

8.2.1 Inclusion Criteria

- Patient is an adult ≥ 18 years old at the time of informed consent.
- Patient has pathologic diagnosis of solid tumor (breast cancer, colorectal, lung, sarcoma, head & neck, sarcoma, genitourinary or gynecological cancer).
- Patients who started chemotherapy (with or without radiotherapy) or planned to receive chemotherapy for at least 12 weeks.
- Patient has an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2.
- Patient with Hb ≤11 g/dL.
- Patient has a Life expectancy at least 6 months.
- Adequate hepatic & renal function defined as a serum aspartate aminotransferase or alanine aminotransferase level that are no more than 3 times the upper limit of the normal range, a serum bilirubin level that is no more than 2 times the upper limit of the normal range and a serum Creatinine level of less than 2 mg per deciliter.
- Patient is able to understand and provide informed consent to participate in the study.

8.2.2 Exclusion Criteria

- Patient has Hb ≤ 8.0 g/dL

- Patient presenting with hematologic malignancy including any of the following: Acute Leukemia, MDS, CML, CLL, Multiple Myeloma, Myelodysplastic syndrome and lymphoma with bone marrow involvement
- Prior gastric surgery.
- Patients on definitive radiotherapy alone.
- Patients **with relevant history (within six weeks)** or clinical evidence of hemolysis or active bleeding **that could, in the investigator's judgment, be a potential cause for the anemia** (no **gross** hematuria, hemoptysis, hematochezia or melena and negative stool for hemoccult-at least one reading)
- Presence of other nutritional anemia; deficiency of vitamin B12 <187 pg/ml and deficiency of Folate < 3.1 ng/ml according to the local laboratory normal ranges
- Patient has Iron overload (Serum Ferritin > 800 ng/ml or Transferrin saturation (TSAT) > 40%)
- Patient is pregnant or lactating.
- Patient has a personal or family history of hemochromatosis.
- Patient has hypersensitivity to any form of IV iron.
- Patient has received red blood cells (RBCs) transfusion or used erythropoietin within 2 weeks of enrollment into the study.
- Patient has received any form of IV iron within the last 12 weeks
- Patient has received oral iron supplements within 1 month of enrollment to the study, except for multivitamin supplements containing less than 30mg iron.

8.3 Subject Withdrawal

Patients are free to withdraw from the study at any time without prejudice or loss of benefits to which they are otherwise entitled. The investigator may remove a patient from the study if, at his discretion, the participation is seen to jeopardize the patient safety or for administrative or behavioral reasons. Neither the investigator nor the study supporting staff will try to coerce patients to continue participating in the study against their will. The withdrawal case with reasons will be documented. Withdrawn subjects will be replaced to have a complete set of 50 analyzable subjects in each strata.

Additionally, patient will be dropped out and will be considered treatment failure if

1 .Receive ESA or blood transfusion for medical reasons not related to the study

2. if they Develop a grade IV toxicity of any kind in the week between the initial and the remaining dose that is possibly related to study drug.

9. Investigational Product

9.1 About Ferinject ® (FCM)[28]

FCM is a polynuclear iron (III)-hydroxide carbohydrate complex. FCM has been designed to enable controlled, systemic release of iron within cells of the reticuloendothelial system, minimizing the risk of releasing large amounts of iron into the serum.

The structure of polynuclear iron (III) hydroxide core resembles that of ferritin: the iron is trapped in the core in a non-redox active form and, therefore, toxic effects from weakly-bound iron are limited. The complex has an average molecular weight of 150,000 Da.

Following IV administration, FCM is metabolized by the RES in the spleen and the liver and the iron is delivered to the bone marrow.

Adverse drug reactions observed during clinical trials and post-marketing experience:

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10000 to <1/1000)
Immune system disorders		Hypersensitivity	Anaphylactoid reactions
Nervous system disorders	Headache, dizziness	Paraesthesia, dysgeusia	Loss of consciousness(3)
Psychiatric disorders			Anxiety(4)
Cardiac disorders		Tachycardia	
Vascular disorders	Hypertension	Hypotension, flushing	Phlebitis, syncope(4), presyncope(4)
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Bronchospasm(4)
Gastrointestinal disorders	Nausea	Vomiting, dyspepsia, abdominal pain, constipation, diahorrea	Flatulence
Skin and subcutaneous tissue disorders		Pruritus, urticaria, erythema, rash(1)	Angioedema(4), pallor(3), and face oedema(3)
Musculoskeletal and connective tissue disorders		Myalgia, back pain, arthralgia, muscle spasms	
General disorders and administration site conditions	Injection site reactions(2)	Pyrexia, fatigue, chest pain, oedema peripheral, chills	Rigors, malaise

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10000 to <1/1000)
Investigations	Alanine aminotransferase increased	Aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased	
Metabolism and nutritional disorders	Hypophosphataemia		

1 Includes the following preferred terms: rash (individual ADR frequency determined as uncommon) and rash erythematous, -generalised, -macular, -maculo-papular, -pruritic (all individual ADRs are frequency determined as rare).
2 Includes the following preferred terms: infusion site burning, -pain, -bruising, -discolouration, -extravasation, -irritation, reaction, (all individual ADRs are frequency determined as uncommon) and -paraesthesia (individual ADR frequency determined as rare).
3 ADRs exclusively reported in the post-marketing setting.
4 ADRs reported in the post-marketing setting which were also observed in the clinical setting.
Note: ADR = Adverse drug reaction.

9.2 Storage, Dispensing and Accountability

The study product will be stored in a secure drug cabinet at KHCC outpatient pharmacy at less than 30 °C. The storage area is separate from the rest of products within the pharmacy. It is access limited to a dedicated Investigational Drug Pharmacist (IDP) who will be responsible to dispense the product for use in the study. Storage conditions will be monitored throughout the study and if there are aberrant conditions they will be reported, justified and corrected as seen appropriate.

Dispensing will be based on paper prescriptions signed by the investigator. The IDP will dispense the required vials to the clinical research coordinator (CRC). The IDP will track product dispensing through the accountability logs. Product documentation for shipment, storage and allocation will be maintained in the pharmacy files until end of study. Documents will then be transferred to the trial master file (TMF).

9.3 Dose and Administration

FCM will be administered based on the following:

Baseline Hb (g/dL)	Body Weight (Kg)	
	<70	>70
<10	1500 mg	2000 mg
≥10	1000 mg	1500 mg

9.4 Stopping Rules

There are no formal stopping rules for the study but should the patient develop anaphylaxis or para-venous leak is observed, the infusion will be interrupted and patient treatment will be left to the attending physician.

10. Procedures and Assessments

All study procedures will be conducted at KHCC. The investigator and supporting study team will be responsible to document all related procedures and assessments done in the appropriate source document and the patient CRFs. All procedures and assessments will support the safety and validity of conclusions drawn from the study protocol.

10.1 Screening and Baseline

Patients will be invited to participate in the study once they are diagnosed as anemic and are planned to receive chemotherapy or radiotherapy within seven days. The Investigator will discuss the study with the patient and acquire a written informed consent before starting any study related procedure. If the patient agrees to participate the following will be carried out:

1. Obtaining medical and oncologic history
2. Physical Examination
3. Vital Signs
4. Laboratory assessments will include:
    - Hemoglobin, reticulocyte count
    - Serum iron, ferritin, total iron binding capacity, TSAT
    - Vitamin B12, folate
    - Creatinine
    - Phosphorous
    - Liver function test including: total bilirubin, ALT, AST, LDH, GGT
    - Serum Hepcidin
    - CRP
    - Pregnancy test

5. Evaluation of ECOG performance status

10.2 Treatment phase

- Patients will receive their prescribed FCM infusion in the KHCC infusion areas or in the inpatients units.
- FCM will be administered as a single infusion if the needed dose is 1000 mg as a short IV infusion, diluted in 250mL of 0.9 saline over 15-30 minutes.

- If the needed FCM dose is > 1000 mg, an initial dose of 1000 mg will be given as above and the remaining dose will be given the week after in a similar fashion if the remaining dose is 1000mg; if the remaining dose is 500mg, then it will be given as a short IV infusion, diluted in 100mL of 0.9 saline over a minimum period of 6 minutes.
- During the infusion, the patient will be monitored for adverse events.

10.3 Follow-up

- Hemoglobin assessments will be carried out every 3 weeks in line with the chemotherapy protocol visits and at week 12.
- Laboratory monitoring of ALT, AST, LDH, Alk-phosphatase, GGT and phosphorous will be done at week-3
- Ferritin level will be repeated at week-12
- A total of four follow-up visits are required for the study: weeks 3, 6, 9 and 12.

Figure 1 Study Scheme

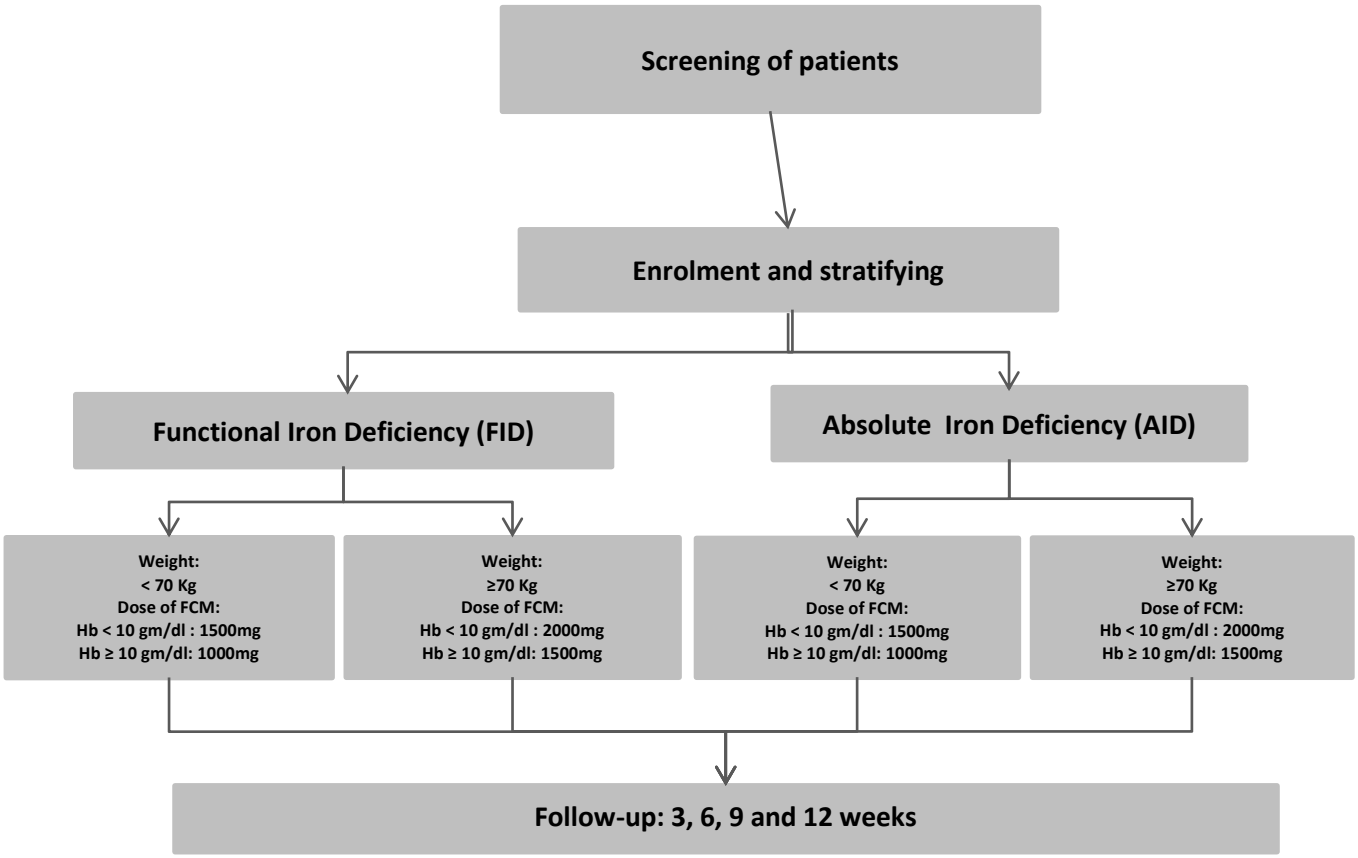

Table 1 Study Procedures Schedule

Procedure	Screening Phase	Treatment Phase		Follow up Phase			
				Week 3 ± 3 days	Week 6 ± 3 days	Week 9 ± 3 days	Week 12 ± 3 days
	Week-0	Week-1	Week-2				
Medical and oncologic history	X						
Physical Examination	X			X	X	X	X
ECOG performance status	X			X	X	X	X
Vital Signs	X			X	X	X	X
Hb	X			X	X	X	X
Reticulocyte count	X						
Serum iron	X						
Serum ferritin	X						X
Total Iron Binding Capacity (TIBC)	X						
TSAT	X						
Hepcidin levels	X						
CRP	X						
vitamin B12	X						
Folate	X						
Creatinine	X						
Bilirubin total	X						
AST	X			X			
ALT	X			X			
Alkaline phosphatase	X			X			
Gamma-glutamyltransferase (GGT)	X			X			
LDH	X			X			
Phosphorous level	X			X			
B-hCG (pregnancy test)	X						
Monitoring of adverse events	X			X	X	X	X
FCM infusion		X	X (when needed)				

11. Adverse events

The best effort will be done by the investigator or study supporting staff to record all adverse events that arise during the study with possible causality and relationship to the study treatment. The proper channels to process these events will be as described in this section. All adverse events reporting will be done with reference to ICH E6: Guidance on Good Clinical Practice[29] and the ICH E2D: Post Approval Safety Data Management[30], and in-house policies.

11.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse Drug Reaction (ADR): all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiologic function.

A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction.

Serious Adverse Events (SAE) or Serious Adverse Drug Reaction (Serious ADR): any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a medically important event or reaction

Unexpected ADR: An ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in local/regional product labeling (e.g. package insert or summary of product characteristics) should be considered unexpected. If it is uncertain whether the ADR is expected or unexpected, the ADR should be treated as unexpected.

An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labeling specifically states that the ADR might be associated with a fatal or life threatening outcome.

11.2 Management of Adverse Events

Standard medical care will be followed in managing adverse events reported during the study in compliance with in house policies and procedures. The PI may ask for additional tests to be done if the adverse event warrants an investigation. The patient will be treated free of charge for all study related events. If the patient is to be discontinued from the study because of the AE he/she will be followed up until the AE abates or returns to baseline.

11.3 Reporting Methodology

All study support staff that are in contact with the patients during the study are responsible to note down any adverse events or complaints reported by patients and report them back to the PI. During their hospital stay, patients will be questioned for adverse events. The team will avoid leading the patient in their adverse event interview. The patient will be asked to describe the severity of their complaint and specify an onset date. Open-ended question will be considered by the study team. The seriousness of the event will be assessed by the investigator and he will determine whether it is expected or unexpected based on the definitions described. Clinical judgment will be used with consideration to the product labeling and known literature.

All AE that are both serious and unexpected will be subject to expedited reporting. For serious unexpected AE with fatal or life threatening consequences, the investigator will notify the JFDA and the institutional review board (IRB) as soon as possible but no later than 7 calendar days from the first time the AE comes to his/her attention. A complete report will be submitted as soon as possible within 8 additional calendar days. Those serious and unexpected ADE/ADR that are not fatal or life threatening will be reported to the JFDA and IRB as soon as possible but no later than 15 calendar days from the first time the AE comes to the knowledge of the investigator with a reasonable suspected causal relationship: A full report will be written to describe the events using the CIOMS I form. The investigator will contact the marketing authorization holder (MAH) of the suspected product with the report in the same manner as would he/she do with the JFDA and IRB if required.

For AE that is not serious whether expected or unexpected do not follow expedited reporting. Within the scope of definitions described above, recording of AE will include description, intensity onset, duration, end and outcome. An evaluation of relationship to the study product will be done according to the following terms: Presence or absence of reasonable possibility that the AE is related to the study drug. AEs will be captured in the case report form. The MAH will not be informed about these AE.

11.4 Follow-up of Adverse Events

All patients will be followed up until recovery or resolution of the AE. The priority for follow-up will be for cases which are 1) serious and unexpected, 2) serious and expected, and 3) non-serious and unexpected. Follow-up information can be through a telephone call and/or site visits (not necessarily related to the predefined study visits or calls). If the patient refuses to provide the information or to come for a follow-up visit it will be indicated in the AE follow-up report. Written confirmation of details given verbally will be obtained whenever possible.

12. Data management

12.1 Case Report Forms

Data for each patient will be compiled in a case report. The case report form used is sufficiently detailed to capture the required information to meet the objectives of the study. Case report form will be retained as part of the TMF and will not have identifiable patient information such as name or medical records number. Case reports forms will be identified with the study ID of the patient.

12.2 Data Entry and the study database

All data from this study that will be used in analysis of primary and secondary endpoints including possible analysis in subgroups of the study population will be transcribed from the subject CRF into an Access database. The transcription of data will be double checked by a member of the support staff that is different from the one entering the data. The database will be designed in house to reflect the subject CRF and the necessary analysis elements. The database will only be used as a reservoir for all the collected data before it is exported into SAS for statistical treatment. Access 2003 or 2007 (2003 compatible mode) database will be used.

12.3 Data Cleaning

Two stages of data cleaning are identified for the study. The first stage is the review of CRFs for missing or misplaced or invalid data before entry into the study database. The second stage is the verification of data entry at the closure of database and before analysis. Queries will be issued by data management to be resolved by the investigator and his team.

Documentation of all queries and corrections made will be maintained in the study masterfile.

13. Statistical Considerations

13.1 Sample Size Calculation

Patients will be recruited over a whole year tentatively between February and December, 2016. It is estimated that 2-5 % of encountered patients are anemic and eligible for enrollment.

Assuming at 90 % power, 5 % level of significance, based on previous pilot study: a proportion of responders of 0.54 and a standard deviation of 1.21, a response rate of 50 % or more being clinically meaningful, and testing for superiority; a minim of 25 subjects are required. To account for a 10 % chance for drop-outs the required sample is adjusted to 47.5 and approximated to the nearest tens. A total of fifty subjects will be required for the assessment. Since, each strata will be analyzed separately, and assuming both follow the same assumptions 50 subjects per strata will be recruited to make a total study sample of one hundred.[31,32].

Recruitment of 100 patients in 10 months is doable.

East 6.3 software was used in the estimation of sample size.

13.2 Statistical Analysis for data presentation

Descriptive statistics will be used to present the two groups baseline characteristics and disease information. in addition to the patient's responses after the whole follow up period.

- Analysis will be done for the two groups separately:
  - **Group I**: Patient with iron-deficiency anemia based on iron studies at base line
  - **Group II**: Patient with non-iron deficiency anemia
- Hb test results will be presented as mean, median and range through all twelve weeks.
- Average percent change from baseline will be used to show the changes of Hb levels. Comparison between means of Hb level will be made between the baseline Hb and Hb levels in the following weeks using Paired T-test.
- Response to IV iron therapy will be assessed in relation to Hepcidin and CRP levels.
- Univariate analysis will be used to assess the effect of patient characteristics and disease information on the response using Chi square test or fisher's exact test.
- Adjusting for all significant factors that may affect the response will be done using Logistic regression.
- Odds ratio out of the Logistic regression will be reported with their corresponding 95% CI.
- A significance criterion of $p< 0.05$ will be used in the analysis.

All analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

13.3 Safety Analysis

Rate and incidence of adverse events will be analyzed and reported. Number of patients requiring ESA or transfusions will be reported using percentages and counts.

14. Quality Assurance and Compliance

14.1 Quality Assurance of Conduct

All study procedures and assessments will be carried following standard policies and operating procedures that are approved by the Quality Assurance Unit of KHCC. The investigator will be responsible to delegate any of the protocol tasks through appropriate channels and documentation through a delegation list. The investigator will be responsible to assure that the study team understand and is properly trained to the requirements and details of the study protocol. The investigator is responsible to show evidence of this training.

14.2 Quality Control of Data

Through-out the study conduct study data will be subject to review by members of the study team that have no direct relation to the obtained data. Data cleaning measures will be considered at the point of data entry. Transcript of data from the CRF or source document to the study database will be checked. Discrepancies found will be collected on data correction forms and appropriate actions taken for them will be documented and those who are found nonredeemable will be justified as appropriate.

14.3 Deviations and Violations

No intentional deviations or violations of the study will be made by the investigator or the study team without going to the appropriate channels for approval (i.e. IRB). Those deviations and violations that occur beyond the control of the investigator or the study team will be documented and reported. Any corrective or preventive actions made will also be described. If the violation or the deviation concerns the study patients the investigator will inform the IRB in writing about the incident as detailed as possible. The investigator judgment will be exercised to whether or not the deviations or violations have adverse effect on the safety of patients or the outcome of the study and hence if there is a need to terminate the patient participation or the study as a whole.

14.4 Retention of Documents

After the study ends, all study documents will be retained at the clinical trial unit office archives for a minimum period of five years post issue of publication. The investigator will then consider if the period of retention needs to be extended any further beyond the retention end date. If the study documents are to be destroyed the destruction will be documented for future reference.

15. Reporting and Publication

15.1 Progress and Final Reports

Progress reports about the study conduct will be prepared at the clinical trials unit. The reports will include breakdown of screening, enrolment and withdrawal status of subjects, as well as, a summary of safety issues and deviations. These reports will be sent to the IRB in each quarter.

A final report of the study conduct and study results will be prepared at the end of the study at the clinical trials unit. The report will be submitted to the IRB after publication of results.

15.2 Publication of Results

KHCC is the sole proprietor of the study data. The Principal Investigator has the right to publish the outcome of the study in any medical journal he sees befitting. The investigator will follow the rules and regulations on authorship defined by KHCC. The principal investigator will be the first and corresponding author. The investigator will follow the CONSORT statement format for reporting clinical trials[33]. Once the publication is made the investigator will provide notice to the IRB about it.

16. Ethical Considerations

16.1 Risk to Benefit Analysis

FCM has been reported to be well tolerated with no significant adverse side effects The most common (≥1/100 to <1/10) adverse effects reported from trials and marketing experience are headache, nausea, hypertension, injection site reactions (pain, bruising, discolorations), mild increase in alanine aminotransferase and Hypophosphataemia. A single dose between 500 mg and 1000 mg is only expected to last 72 hours (terminal half-life between 7 to 12 hours). Adverse reactions, if happened, are transient and can be managed.

On the other hand, if a short course of FCM (one or two treatments) proves to be effective and hepcidin and/or CRP are proved as effective predictors of response; we will then have an effective treatment for anemia and we will be able to find methods to make the distinction between patients who are likely to respond and those who are not.

16.2 Institutional Review Board

The IRB of KHCC will review the study protocol and provide their favorable opinion on the study conduct. The study will not start without gaining the IRB approval first. The PI is responsible to assure that all documents necessary for the IRB review and issue of judgment will be supplied without delay. The investigator will not do changes to an already approved protocol without discussing it first with the IRB through a written amendment request unless it was necessary to remove an immediate hazard to the study patients or the change was of a logistical ground such as the change of phone numbers.

The investigator will also be responsible to report all AE to the IRB according to KHCC policies and procedures. The final outcome of the study will be provided in a written summary report within a reasonable time span.

16.3 Ethical Conduct of the Study

The study will be conducted in accordance with ethical principles that have their origins enunciated in the Declaration of Helsinki, adopted by the General Assembly of the World Medical Association (WMA), Helsinki, Finland (1964) and amended by the 59th WMA General Assembly, Seoul, 2008[34]. The study will be conducted in accordance with the protocol and the ICH guideline on Good Clinical Practice[26] topic E6.

16.4 Informed Consent

Patients will not be allowed to participate in the study and carry out any of the study procedures before they have been properly informed of all aspects of the study, roles and expectation, risks and benefits through a thorough consent procedure. The study patients will be required to sign a consent form establishing their agreement to participate in the study and that they have understood all implications and attributes of the study. If for reasons of illiteracy the patient is unable to sign the consent him/herself, a legally accepted representative will be required to attend the consent procedure and sign on behalf of the patient's guardian. The signed consent document will be retained in the study file and another signed copy of the consent will be given back to the patient.

Patients will not be coerced to participate in the study by the investigator or the study team. The patients will be given the freedom to review and consider the study before they provide their decision. The decisions to participate or not will neither affect the patients in terms of care and treatment nor will it deprive them from benefits to which they are entitled. Patients will be free to withdraw at any time without any prejudices held against them in any way or to their right to appropriate counseling and management of their case.

The consent form will be prepared in the Arabic language that is considered the native language in Jordan. The level of the text will be prepared at that of an 8th grader. The consent will fulfill the elements of informed consent specified in the US FDA code of federal regulation (CFR) on the protection of human subjects 21 CFR Part 46.116.

16.5 Confidentiality and Privacy

Patients will be introduced to the study during the hospitalization or their out-patient clinic visits. The study discussion and consent will be held in a private area such as an office or in the patient bedroom.

Throughout the study the patients' identity and data collected for the study will be kept confidential among the study team delegated by the investigator to conduct the study. The patient will be addressed with an appropriate code and with their initials in all study documentation as appropriate. Access to the patient identity and data will be restricted to the study team and the IRB.

16.6 Rights and Liabilities

For all study related events regardless of causality, patients have the right for appropriate treatment and medication to resolve the event free of charge. Events that are unrelated or are disease related will not be covered or considered for coverage. No one from the study team, investigator or the KHCC will be responsible for self-inflicted injuries, injuries resulting from violating protocol or the study team instructions

that are in the best interest of the patient. Patients coverage for adverse events will be through an arranged insurance contract.

16.7 Premature Termination of the Study

The study will be terminated if one of the following is met:

1) The investigator has decided to stop the study due to high incidence of AE to assure the safety of the patients.

2) If the recruitment rate was inefficient or sufficient for the study endpoints to be met.

3) The IRB has issued a decision to abort the study for any reason.

The decision to end the patient participation or end the whole study prematurely will be in writing regardless of who made that decision and will be conveyed to the other parties. The patients will have the appropriate follow-up measures done for them before their files are closed.

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