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Review Article

Challenges in the Management of Chemotherapy Related Anemia

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Abstract

Chemotherapy-induced anemia (CRA) was reported with methotrexate, when it was used in early 50sto treat cancer, and cure patients with choriocarcinoma. Subsequently, CRA has been observed with other chemotherapeutic agents. Patients with CRA have local tumor control from hypoxia and subsequent resistance to chemotherapy and radiotherapy with decreased overall survival. Therefore, CRA requires appropriate intervention. However, there are difficulties in diagnosis and management of CRA, because of the multifactorial etiology of anemia in cancer patients. In spite of several randomized controlled clinical trials and systematic reviews, there is still lack of standardized approach to the management of CRA. We will review the pathophysiology of CRA especially the role of Hepcidin, and discuss algorithm for diagnosis and treatment of CRA. The purpose of this article is to help the clinician stratify the management based on review of available evidence, which may change as future data emerges.

Keywords: Chemotherapy; Anemia; Iron; Erythropoietin; Blood transfusion; Therapy

Pathophysiology of CRA

Chemotherapy-related anemia occurs in about 75% (30%-90%) of cancer patients receiving chemotherapy [1,2]. There is direct inhibition of erythropoiesis by cytokines (interleukin-6, tumor necrosis factor α, interferon gamma and interleukin-1). Interleukin-6 increases production of hepcidin by liver, causing CRA (Figure 1).

Hepcidin is incriminated in the pathogenesis, and may soon find its place as a promising tool in the diagnosis and management of iron deficiency and CRA [3-5]. Hepcidin maintains iron homeostasis [6]. It is a25-amino acid peptide produced by the liver secondary to an inflammatory state. Hepcidin is produced by hepcidin anti-microbial peptic gene (HAMP) in chromosome 19 [7]. Over expression of this gene is seen with hematological and non-hematological cancers secondary to release of interleukin-6 [8]. Hepcidin inhibits the release of iron from macrophages in bone marrow by suppressing ferroportin Figure 1. Ferroportinhelps transfer of iron from gastric mucosa to transferrin, the biological iron transporter of blood [8]. Functional deficiency of iron results from release of cytokines resulting in increased production of hepcidin from the liver. Elevated level of hepcidin is seen in solid tumors including prostate, kidney, brain, lung, breast, liver and ovarian cancers [9-12]. Hepcidin levels are also increased in Hodgkin's lymphoma, non-Hodgkin's lymphoma, acute lymphoblastic/myeloblastic leukemia and myeloma [7,13,14]. However, in hematological malignancies, an interleukin -6independent mechanism, mediated by increased bone morphogenetic protein (BMP-2), a regulator of hepcidin transcription is also described [7]. Hepcidin expression is suppressed in liver when there is infiltration by the tumor [7].

Clinical Features and Assessment of Patients with CRA

The initial workup should include a detailed history. The common symptoms include: effort dyspnea, syncope, headache, vertigo, chest pain, fatigue interrupting activities of daily living, and history of blood loss from gastrointestinal/genitourinary tract. Patients need focused physical examination for evidence of infection from central line, chest or urinary tract. Hematinic work up must include serum iron, iron binding capacity, ferritin, serum B12, red cell folate, evidence of hemolysis including reticulocyte count, LDH, haptoglobin, assessment of renal and liver function tests, coagulation profile to exclude acute or chronic DIC, ultrasound abdomen for splenomegaly and blood smear for evidence of toxic changes (vacuoles, hyper- granulation) of polymorphs, leukoerythroblastic blood picture, fragmentation of RBCs or other evidence of hemolysis.

Difficulties Encountered in Management of CRA

It was traditionally felt that for CRA, no specific intervention, including blood transfusion, is needed unless hemoglobin concentrations declined to a low level (<7 g/dL) or the patient developed symptoms of shortness of breath, chest pain or palpitation (Table 1) [15]. The anemia that did not reach the transfusion trigger was considered unimportant.

The emerging data suggests that CRA that did not reach the transfusion trigger, still causes fatigue, which has an adverse impact on quality of life [16]. The incidence of fatigue occurs in about 80% to 90% of patients receiving chemotherapy [17]. However, fatigue is very subjective. Symptoms mimicking fatigue may be secondary to psychological and emotional causes including depression, breakdown of interpersonal relationship or systemic illness including nausea, vomiting, cardiac, renal and hepatocellular dysfunction. There are validated functional assessment scales to assess fatigue in CRA, but these are largely unused [18,19]. The difficulties in management of CRA include: clinical heterogeneity, multifactorial etiology of

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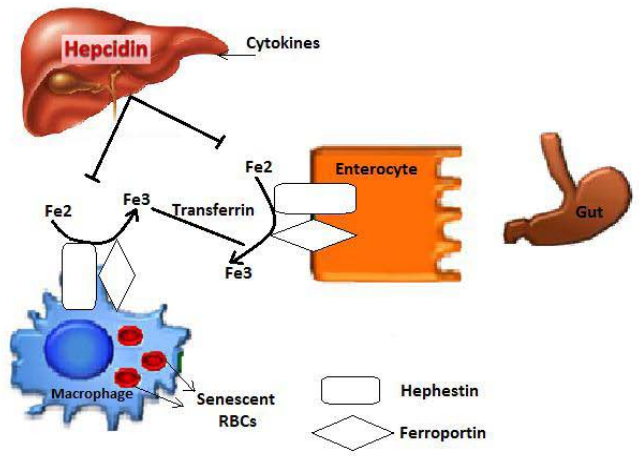

Figure 1: Role of Hepcidin in CRA.

Table 1: Grading the severity of CRA.

Severity	WHO	NCI
Grade 0 (WNL)	>11.0 g/dL	14.0-18.0 g/dL for men12.0-16.0 g/dL for women
Grade 1 (mild)	9.5-10.9 g/dL	>10.0 g/dL
Grade 2 (moderate)	8.0-9.4 g/dL	8.0-10.0 g/dL
Grade 3 (serious)	6.5-7.9 g/dL	6.5-7.9 g/dL
Grade 4 (life threatening)	<6.5 g/dL	<6.5 g/dL

WHO: World Health Organization; NCI: National Cancer Institute

anemia in cancer patients, difficulty in incorporating the standard assessment tools of fatigue and Quality-Of-Life (QOL), appropriate time to intervene and side effects associated with intervention (blood transfusion, erythropoietin, intravenous iron). Lack of consensus for management from international practice guidelines makes CRA, a challenging clinical entity [20].

What are the Treatment Options Available for CRA? Review of Evidence

In the management of CRA, the available treatment options include: Red blood cell transfusion, ESA and iron therapy. For serious and life-threatening CRA, blood transfusion is the treatment of choice -Table 1. For less severe types of CIA (Hb. <10dL), the FDA approved erythropoiesis stimulatory agents (ESA) in 1993. Following worsened health outcomes associated with the use of ESA, the Food and Drug Administration (FDA) in 2007, made substantial revisions for use of ESA because of increased risk of tumor progression or reduced survival in patients with cancer [21,22]. The NCCN and FDA have restricted the indications for ESA with or without iron supplementation in CRA, for patients with cancer, only when cure is not the ultimate aim of treatment. While IV iron may be beneficial in CRA, it is not uniformly approved by most of the international clinical practice guidelines in Oncology [23].

When is Red Cell Transfusion Needed in CRA?

The transfusion guidelines of the American Association of Blood Banks (AABB) do not make a specific recommendation for a transfusion threshold in patients with hematological or oncological disorders [24]. Nevertheless, many physicians follow the AABB recommendations of restrictive hemoglobin transfusion threshold of 7 g/dL in hemodynamically stable hospitalized adult patients [24-26]. NCCN (Version 2.2018) outlines three general categories: 1) asymptomatic without significant comorbidities, for which observation and periodic re-evaluation are appropriate; 2) high risk (progressive decline in Hb. with recent intensive chemotherapy or radiation) or asymptomatic with comorbidities (cardiac disease, chronic pulmonary disease, cerebral vascular disease), for which transfusion can be considered; and 3) symptomatic, for which patients need transfusion. The need for RBC transfusion in CRA should be based on overall clinical context, comorbidities including underlying vascular disease, patient preferences, and alternative specific interventions, when making decisions regarding transfusion in individual patient [24]. There are no specific evidence based guidelines for patients with thrombocytopenia, chronic transfusion-dependent anemia or patients with acute bleeding symptoms [24, 27-30]. Higher hemoglobin thresholds may be needed for patients with severe thrombocytopenia, who are at increased risk of bleeding, as experimental evidence suggests that anemia may aggravate thrombocytopenia induced bleeding [31].

How do we Dose ESA in CRA?

Centers for Medicare and Medicaid Services (CMS) have stringent guidelines for ESA use in metastatic cancer (cms.gov). The hemoglobin level immediately prior to initiation or maintenance of ESA treatment should be <10 g/dL (the hematocrit <30%). The starting dose for ESA treatment should be no more than 150 U/kg/three times weekly for erythropoietin and 2.25 mcg/kg/weekly for darbepoetin alpha. When hemoglobin (Hb.) rises <1 g/dL (hematocrit rise <3%) compared to pretreatment baseline over 4 weeks of treatment and whose Hb. level remains <10 g/dL after the 4 weeks of treatment (or the hematocrit is <30%), the dose may be increased once by 25%. Continued use of the drug is not reasonable and necessary if the hemoglobin rises <1 g/dL (hematocrit rise <3%) compared to pretreatment baseline by 8 weeks of treatment. The ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy. About 50% to 70% of patients treated with ESAs in clinical trials of CIA, responded to treatment as measured by increment in Hb [32-36].

How do we Diagnose CRA in the Setting of Iron Deficiency?

Diagnosis of Iron deficiency is difficult in CRA, as iron deficiency may be absolute (true) or relative (functional). Absolute iron deficiency may develop from mucosal bleeding and during chronic ESA administration due to a progressive shift of iron stores to the erythron [37]. Functional iron deficiency occurs when the body iron stores are normal (or even increased), but iron supply to the erythroid marrow is inadequate in the initial phase of RBC regeneration, after the administration of ESA to subjects [38]. This is relevant in any condition causing anemia of chronic inflammation. Here, the serum iron and transferrin saturation are low, serum ferritin is normal, and iron procurement by transferrin is not adequate [39]. Absolute Iron deficiency is diagnosed when reticulocyte hemoglobin content is <28 pg (now incorporated with the anemia panel in most of the labs.) or

Table 2: Trials of ESA with IV iron in CRA.

Study	No.	Treatment	Duration	Conclusion
Auerbach et al. [52]	157	ESA /ESA+Po Fe./ESA+IV Fe.	6 W	Response
Henry et al. [53]	129	ESA /ESA+Po Fe./ESA+IV Fe.	4W	Response
Hedenus et al. [46]	67	ESA /ESA+IV Fe.	15W	Response
Bastit et al. [45]	678	ESA+Po Fe./ESA+IV Fe.	10W	Response
Pedrazzoli et al. [47]	252	ESA/ESA+IV Fe.	12W	Response
Auerbach et al. [54]	402	ESA/ESA+IV Fe.	15W	Response
Steensma et al. [55]	814	ESA /ESA+Po Fe./ESA+IV Fe.	15W	No benefit
Steinmetz et al. [48]	286	ESA /ESA+Po Fe./ESA+IV Fe.	12W	Response
Macciò A et al. [56]	148	ESA+PO Fe./ESA+IV Fe.	12W	No benefit

ESA: Erythropoietin; PO Fe: oral iron; IV Fe: Intravenous Iron

with an elevated soluble transferrin receptor assay (0.76-1.76 mg/L) [40,41].

Oral or Intravenous Iron in CRA? REVIEW of Evidence

Petrelli, et al. [42] in their meta-analysis of IV and oral iron in CRA, reported that oral iron failed to increase either the hematopoietic response or the transfusion rate. Another meta-analysis compared IV iron with oral iron with ESA in CRA, and found improved hematopoietic response and reduced need for RBC transfusions with IV iron [43]. The benefit of IV iron with ESA for patients with metastatic cancer with improvement in their hematological status, was again confirmed in a Cochrane Review [44]. The response to IV iron was attributed to the functional iron deficiency that occurs in the initial phase of erythropoietin therapy (secondary to increased red cell production depleting the iron stores), not able to keep pace even with several fold increased iron absorption from the gut by ESA [39]. However, the trials included in the meta-analysis had different end-points and criteria for patient selection. Moreover, the eligibility criteria varied, from baseline serum ferritin of <10 ng/mL to 900 ng/mL, and iron saturation of <15% to 60%thus providing little, if any, information to be translated in the everyday clinical practice [45-47]. A recent meta-analysis showed no difference in quality of life with iron supplementation in CRA [44]. Not included in any of the meta-analysis are the three IV iron alone (without ESA) trials in CRA. They all had increment of Hb. (1.3 g/dL –1.8 g/dL), with at least one trial documenting a significant reduction in the transfusion rate (63.6 to 22.7 %) [48-51]. However, in the IV iron only trials, patients received IV iron regardless of their initial iron status [23].

What is the Ideal Dose and Type of IV iron in CRA?

Intravenous iron is well tolerated, but the total dose of IV iron in the trials varied from 750 mg- 3000 mg and there was no maximum limit to the dose of IV iron [23]. In most of the trials, IV iron was given when the chemotherapy regimen exceeded eight weeks, but the duration of IV iron therapy in the trials is wide-ranging. The type of IV iron, dose and treatment regimen in the trials varied widely. This includes iron sucrose 100 mg IV weekly, iron sucrose 200 mg IV every 2-3 weekly, sodium ferrous gluconate 125 mg IV weekly, low molecular weight iron dextran 100 mg IV weekly and low molecular weight iron dextran as total dose IV infusion [57]. Mhaskar et al. [44], in their Cochrane Review, reported that the type of IV iron (dextran versus gluconate versus sucrose) did not have an impact on hematopoietic response.

Clinical Practice Guidelines

NCCN (National Cancer Committee Network) guidelines (version 2.2018) has endorsed IV iron to be considered for CRA, with serum ferritin up to 1000 ng/mL or till iron saturation reaches 50%. The NCCN (NCCN version 2.2018) guidelines recommend that clinicians consider repeating iron studies if the MCV is <80 fL, or if evidence of hypochromic red blood cells is seen in the peripheral blood. European Organization for Research and Treatment of Cancer (EORTC) has clearly stated that there is no role for oral iron with ESA in CRA, suggesting ESA with the addition of intravenous iron is needed for improved hematological response [58]. Other practice guidelines have not uniformly accepted IV iron in patients with CRA. The current ASCO/ASH guidelines have not endorsed IV iron, because of the insufficient evidence to consider IV iron as a standard of care in CRA [59]. According to the Canadian guidelines, the provision of parenteral iron in CRA with ESA is to be considered for patients with functional iron deficiency (serum ferritin >100 ng and iron saturation >15%) [57]. The European Society for Medical Oncology (ESMO) has advised IV iron, only for patients with absolute iron deficiency [60]. The role of IV iron in management of CRA, is still unsettled [59].

Monitoring Intervention in CRA

Monitoring intervention appears to be difficult because of vague symptoms, but quality-of-life outcome is a measurable target. Cancer-related fatigue is multifactorial, under-reported and under-treated [61-63]. NCCN Guidelines Version 2.2017 defines cancer-related fatigue as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment, which is not proportional to recent activity. The tools to assess quality-of-life outcome and to monitor response to therapy include: Brief Fatigue Inventory [64], EORTC QLQ -C30 questionnaire [65], Fatigue questionnaire [66], Visual Analogue Fatigue Scale [67], Fatigue Symptom Inventory [68] and NCCN Problem List.

Management

There are no standard guidelines for management of chemotherapy related anemia. Treatment of chemotherapy related anemia is based on clinical state of the patient (adjuvant or metastatic setting), rapidity of the needed response (based on vitals and comorbidities) and adherence to CMS guidelines in use of erythropoietin, iron supplementation (either by mouth or IV route) and judicious use of PRBCs.

In the comprehensive data collected from the National Cancer Institute (NCI)-surveillance epidemiology and end results (SEER) and Medicare-linked database, the combination of ESA and other agents including trastuzumab showed no negative impact on long-term survival of metastatic cancer patients [72]. The detrimental effect of ESA in patients with metastatic breast cancer was seen when Centers for Medicare and Medicaid Services (CMS) guidelines were not strictly adhered to [73].

Conclusion and Future Directions

Management of CRA is challenging, as there are no internationally accepted guidelines for management of CRA. However, we have made rapid strides in understanding the pathophysiology of CRA. The primary aims of treatment in CRA are to avoid blood transfusion and to improve anemia related symptoms .With the restrictions in ESA, IV iron on its own, may be an alternative. The expected overall survival of all cancers is on the upward trend according to a report released by FDA in 2017. Moving forward, we need a risk adopted strategy for management of CRA. In the absence of "Consensus Statement", accumulating evidence suggests that treatment of CRA should be based on clinical severity, stage of the disease, application of reticulocyte hemoglobin in the diagnostic panel and utilization of validated predictive biomarker hepcidin in CRA. Herein, we have attempted to provide a rational approach to the management of CRA, acknowledging that there are no evidence based algorithm available for this clinical entity.

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