Chemotherapy-Induced anemia in adults and treatment.

Sadraldin Ali[1], Ahmed Farhan[1], Ibrahim Qader[2], Shahla Mohammed[1]

[1]*Biology Department, College of Science, University of Raparin, Rania, Sulaymaniyah, Iraq*
[2]*Department of Physics, College of Science, University of Raparin, Rania, Sulaymaniyah, Iraq*
[3]*Department of Medical Laboratory Science, University of Raparin, Rania, Sulaymaniyah, Iraq*

Journal of Bursa Faculty of Medicine
e-ISSN: 2980-0218

Review

Clinical Sciences

Received
February 14, 2024
Accepted
April 19, 2024
Published online
May 4, 2024

J Bursa Med 2024;2(2) 34-49

ABSTRACT

Chemotherapy-induced anemia is the predominant adverse event observed in individuals undergoing cancer treatment, resulting in a reduction in red blood cells and hemoglobin levels. This condition manifests through indicators such as diminished quality of life and fatigue. Effective approaches for managing recurrent chemotherapy-induced anemia encompass the use of erythropoietin stimulating agents, blood transfusions, and intravenous iron supplementation. Each of these interventions presents distinct pros and cons, with the selection of a particular treatment modality contingent upon the severity of anemia and the duration of malignancy. A comprehensive review of scholarly literature reveals a high prevalence of anemia among cancer patients receiving chemotherapy. Ongoing research endeavors are focused on the development of pharmacological agents for cancer treatment that are devoid of adverse effects, particularly concerning anemia, a common complication associated with this therapeutic approach.

Keywords: Anemia, Cancer, Chemotherapy, Erythropoietin.

Anemia, derived from the Greek word "anaimia" meaning "lack of blood," refers to a condition where the blood's capacity to transport oxygen is diminished. This condition is often associated with malignancy [1]. There is no more common and persistent hematological disorder than anemia in those with cancer [2]. Chemotherapy-induced anemia (CIA) results from bone marrow infiltration disrupting erythropoiesis, malignant metastasis to normal tissue causing lack blood and inflammation-induced functional iron deficiency [3].

One important side effect of chemotherapy is CIA, which might delay or limit therapy and increase fatigue and quality of life reduction [4]. Furthermore, the intricate landscape of CIA treatment modalities will be scrutinized, ranging from traditional approaches such as blood transfusions and erythropoiesis-stimulating agents (ESAs) to contemporary strategies informed by advancements in molecular and cellular biology [5]. A thorough review of the changing field over the past 50 years can be obtained by analyzing the literature on chemotherapy-induced anemia as shown in Figure 1. Chemotherapy-induced anemia publicationexamining publishing years can be organized to show significant advancements, patterns, and changes in the direction of research at certain points in time.

Foundation and Recognition from the 1970s-1990s Publications during this peri-

How to cite this article
Braim S, Shallal A, Qader I, Shahla Mohammed. Chemotherapy-Induced anemia in adults and treatment. J Bursa Med 2024;2(2);34-X

Address for correspondence
Sadraldin Ali Braim, University of Raparin, Rania, 46012, Sulaymaniyah, Iraq
Email: sadradinali02@gmail.com

Available at https://dergipark.org.tr/tr/pub/bursamed

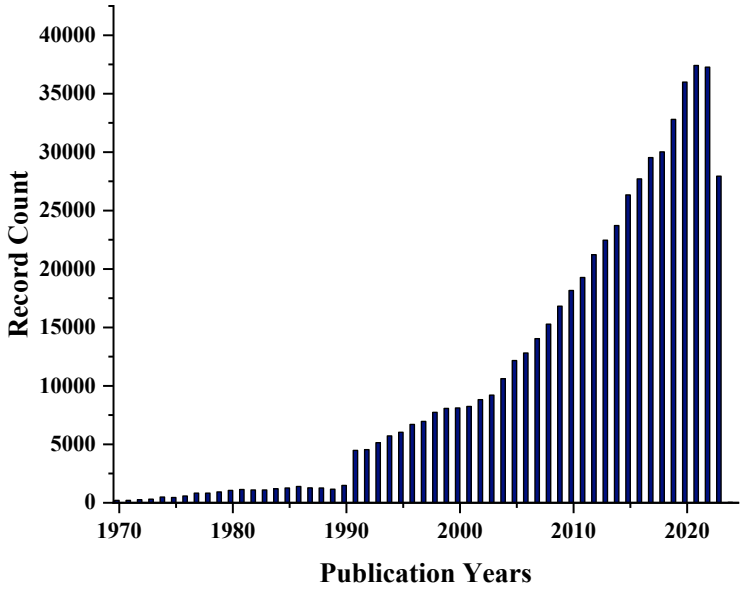

Figure 1. Chemotherapy-induced anemia publication from 1970 t0 2020
Source: Web of Sciences, Keywords: Anemia, Cancer, Chemotherapy, Erythropoietin.

od investigating the prevalence of anemia in patients with cancer, 1990 to 2020 the quality of life, and erythropoiesis-stimulating agents as a treatment this period might also have seen debates and discussions regarding the appropriate utilize of ESAs in patient and focus on produce new strategies for prevent anemia when using chemotherapy.

A five-decade timeline of publications summarized shown in Figure 2 a progression from basic statements of anemia prevalence to a more complex knowledge of its complex nature. The bar chart shows that early publications from 1970 to 1990 decreased but after that, the process of research about the widespread of anemia in cancer patients increased and reached a top in 2021.

The timeline documents turning points in the development of new treatment techniques advances in medicine, and an increasing understanding of the sig-

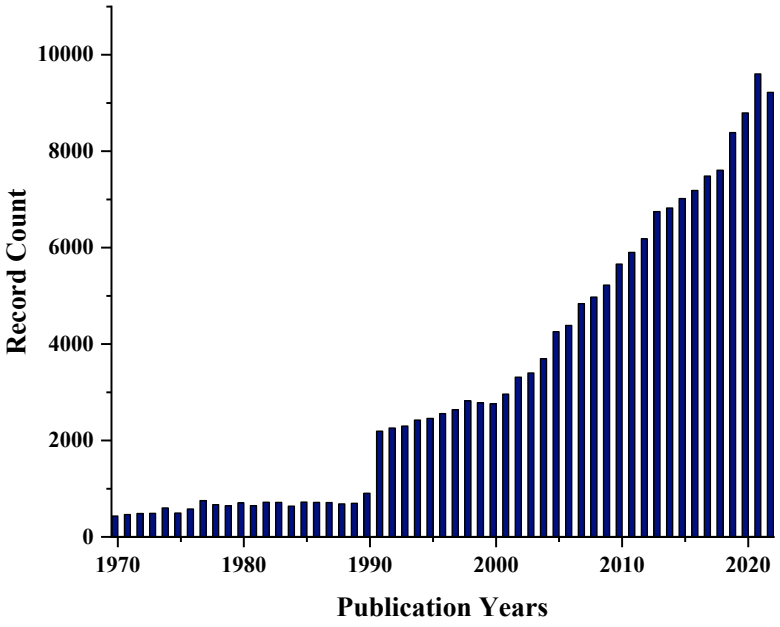

Figure 2. Anemia research landscape over time yearly publication count
Source: Web of Sciences, Keywords: Anemia, Cancer, Chemotherapy, Erythropoietin.

nificance of treating anemia as a critical component of cancer patient care. There may have been a stronger focus on patient-centered care and individualized treatment in the latter half of the study period, which runs from 2010 to 2020. Articles may provide individualized methods of treating anemia depending on a person's traits, biology, and reaction to treatment. Improvements in nutritional techniques and supporting care were probably made at this time.

1. Cancer Related Anemia

The pathogenesis of cancer-associated anemia, which includes radiation-induced anemia (RIE), chemotherapy-induced anemia , and persistent renal failure, comprises several components [6]. Anemia secondary cancer directly results from the original tumor infiltrating healthy organs and producing hemorrhage, marrow infiltration preventing the producing of red blood cells, or chronic inflammation resulting in low levels of iron [7]. Cancer-induced anemia is a typical side effect of myelosuppressive treatment such as chemotherapy, whether administered separately or in combination with radiation the pathogenesis of cancer induced anemia show in Figure 3 [7]. Most elderly cancer patients can be diagnosed with chronic kidney disease , this might result from the decline associated with aging, chemotherapy, and kidney injury from tumor penetration [8].

Anemia can be caused by underlying co-morbidities including inflammatory illnesses, hemolysis, coagulation abnormalities, genetic diseases, renal insufficiency, or nutritional deficiencies [9]. The pathophysiological origin of anemia in patients who have cancer can be divided into three main categories reduced red blood cell (RBC) production, destruction of RBC, and blood loss [10].

1.1 Reduced RBC Production

Lower erythropoiesis due to a variety of causes is the main mechanism behind of cancer-induced anemia, and also chronic renal disease and acute renal injury is one of several causes of decreased erythropoietin production [11, 12]. Inadequate intake of total iron, vitamin B 9, and vitamin B12 in the dietary regimen, or damage to the bone marrow resulting from conditions such as myelodysplasia, bone metastases, or myelosuppressive chemotherapy [13, 14]. Patients with thymomas, leukemias, pure red cell aplasia may occur in lymphomas or tumors due to cytokines related to the tumor or, in extremely rare cases, because to the development of anti-erythropoietin antibodies after the administration of external a hormone called erythropoietin [15, 16]. Furthermore, anemia is a common presentation for patients whose cancers originate from hematopoietic progenitors [7]. The excessive multiplication of blast cells in the bone marrow may contribute to this condition, since they displace the non-malignant cell population [17]. It is thought

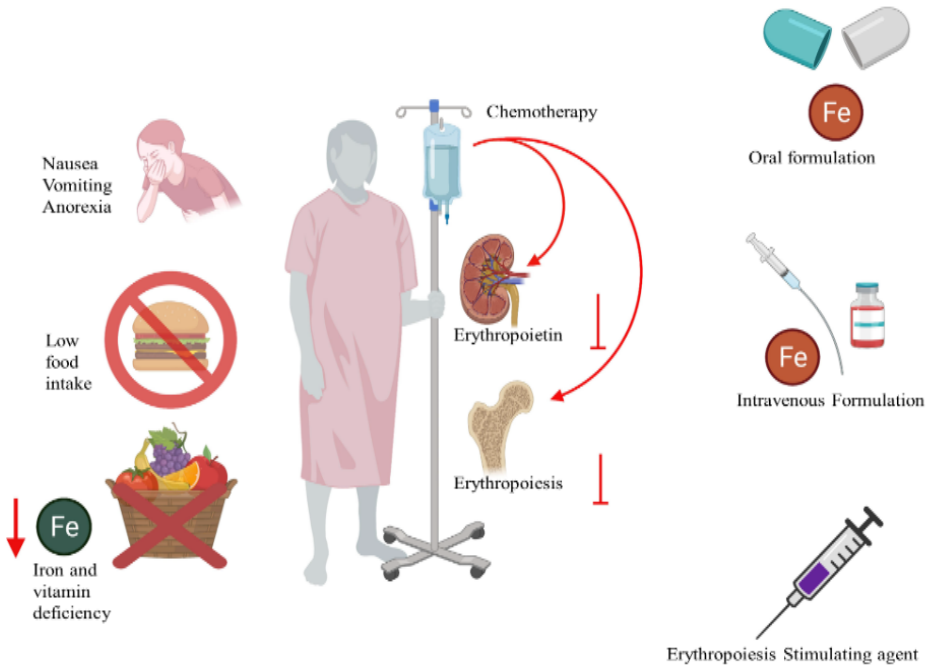

Figure 3. Pathogenesis of chemotherapy-induced anemia [42]

that normal erythroid blast-forming units and islands rely on interactions with stem cell factors and bone marrow stromal cells to sustain their differentiation, proliferation, and division [18]. However, this phenomenon hinders them from doing so [19, 20].

1.2 Destruction Red Blood Cell

Microangiopathic processes, such as erythrophagocytosis in histiocytic tumors, are among the mechanisms that causes damage the red blood cell as the result anemia will be occur [21]. Another condition that may cause the death of red blood cells is hemolytic disease anemia, which is common in persistence lymphocytic leukemia [22]. Hematopoietic cell sequestration often occurs in Hypersplenism associated with myeloproliferative neoplasms, lymphoid malignancies, cancer that invade the spleen, and tumors that induce portal hypertension [23].

1.3 Blood loss

Anemia resulting from the loss of red blood cells may be caused by treatment-related causes, such as blood loss after surgery or repeated blood drawing for laboratory testing[24]. As well as tumor-related bleeding seen in cases of uterine cancer or gastrointestinal malignancies [25]. Gynecological, genitourinary, and gastrointestinal malignancies can all result in disease-related blood loss. Both radiation and chemotherapy have the potential to affect the immune system and prevent erythropoiesis, some treatments, however, may result in anemia at a higher rate than others. Anemia of chronic illness is the term used to describe the anemia that affects a significant percentage of cancer patients who have no known etiology [26].

Unfortunately, not all medical professionals regularly measure, record, or even survey symptoms associated with anemia. Additionally, the severity and defining thresholds are not uniform. The absence of consistent, objective grading schemes for anemia and associated various expressions make quantitative assessment difficult. While some research describes anemia as a decrease in baseline hemoglobin, using recombinant human erythropoietin treatment, or requiring blood transfusions [27]. The toxicity grading system that is utilized to identify anemia is not documented by others [13]. The following anemia grading system was proposed by the National Cancer Institute Anemia [28] . An amount of hemoglobin below 12 g/dl can be regarded as suggestive of anemia, as defined by the World Health Organization and National Cancer Institute show in Table 1 severity scale for anemia [29]. The scale is made up of the following grades.

According to the European Cancer Registry's Anemia Survey a large-scale study, 39% of the 15,367 individuals who had chemotherapy were found to have anemia after being observed for a period of six months [30]. Anemia was defined as having a hemoglobin level below 10.0 g/dL, only 39% of these individuals received treatment overall, mostly with blood transfusions or erythropoietin-stimulating drugs [31]. The etiology of cancer-related anemia is complex and frequently difficult to identify, with several factors often implicated [32].

Although the exact underlying mechanisms causing this kind of anemia are unknown, it is believed that they involve the activation of cytokines such as tissue necrosis factor, interleukin-1(IL-1), and interferon-gamma γ, these cytokines may endogenous erythropoietin synthesis to be suppressed and enable iron consumption [33]. Between 30% to 90% of cancer patients are thought to have anemia at some point throughout their illness [34] .

Chemotherapy regimens that are not started or are not finished on time can have an impact on survival due to anemia, adequate oxygen levels are also necessary to prevent cytotoxicity caused by radiation therapy and certain chemotherapy regimens [35]. Because tumor hypoxia renders malignancies resistant to chemotherapy and radiation, it might perhaps contribute to the tumor's lack of response [36-38]. An imbalance between oxygen intake and delivery leads to tissue hypoxia, arises in solid tumors when the oxygen consumption rate of the neoplastic cells surpasses the ox-

Table 1. Scale of anemia in cancer patients [29, 135]

Scale	State	Range
Grade 0	Typical	Men (14-18) g/dL, Women (12-16) g/dL
Grade 1	Slight	Men (10-14) g/dL, Women (10-12) g/dL
Grade 2	Intermediate	8–10 g/dL
Grade 3	Intense	6.5–8 g/dL
Grade 4	Potentially fatal	<6.5 g/Dl

ygen supply available to them [39].

The structural and functional abnormalities of the tumor microcirculation might lead to inadequate blood flow, which can also be attributed to an increased diffusing distance, which limits the amount of oxygen available [24]. Reduced blood oxygen-carrying capacity due to anemia from the tumor or its treatment can exacerbate tumor hypoxia can modify the rate of cell division after radiation therapy or chemotherapy by influencing the cell cycle and proliferation kinetics [40]. Research has also demonstrated that persistent tumor hypoxia might, by clonal selection and genetic alterations, further promote the advancement of malignancy and perhaps heighten aggressiveness [41].

2. Immunological Alteration in Cancer Patients

Immunological changes that occur as the neoplastic disease develops have a significant influence on the patient's clinical circumstances and may even result in the patient's mortality is called cancer cachexia syndrome [42]. Apart from anemia, various symptoms related to multiple organs and processes are brought on by the immune system's alterations [43]. These include weight loss, anorexia, vomiting, fatigue, nausea elevated energy metabolism with changes in glucose, lipid, and protein metabolism, and immunosuppression, heightens susceptibility to infections [44].

It is impossible to pinpoint the exact moment these alterations occur, but it is known that the patient's immune system and cancer interact to cause these changes [45]. Different soluble factors, or cytokines, are produced by inflammatory cells, lymphocytes, and mesenchymal cells that have been activated, certain cytokines have the ability to stimulate or repress certain cell types [46].

When it comes to the cell-mediated immune response, interleukin-1(IL-1), interleukin-6(IL-6), and tumor necrosis factor alpha (TNF-a) are release these molecules also function as second messengers for the creation of interleukin-2(IL-2) which is essential for the regulation of the immune response against cancer [47].The degree of immunological dysfunction is correlated with the stage of malignancy [48]. Linked to the quantity of acute phase proteins and other inflammatory cytokines, especially IL-6 [49]. It is reasonable to suppose that compromised lymphocyte activities are a stand-in for a variety of functional alterations, the most significant of which are the immunosuppressive effects of cytokines released from macrophages and modifications to energy metabolism that can lead to an oxidative stress state. Our earlier research demonstrated that cancer patients are significantly more likely to have elevated oxidative stress [50, 51].

Notably, inflammatory cytokines have specific immune-modulatory properties, but they also vital influence in the pathophysiology of the primary metabolic abnormalities [42].

2.1 Specific Actions of Proinflammatory Cytokines

The cytokines IL-1, TNF-a, and IL-6, which are known to lead to inflammation, have been shown to have a wide range of effects on erythropoiesis, including decreased erythroid precursor proliferative response, increased macrophage destruction of erythrocytes, and decreased erythroid precursor response to EPO [52]. Furthermore, patients with advanced cancer experience several nutritional and metabolic abnormalities that are mostly brought on by the persistent action of these same cytokines , notably promote inflammatory cytokines related to the development of cancer related anemia by affecting nutritional status and energy metabolism IL-1 may reduce erythropoiesis by particularly reducing the replication and maturation of burst-forming unit-erythroid (BFU-E), and colony-forming unit-erythroid (CFU-E) cells precursors decreasing the expression of the Erythropoietin (EPO) receptor and impairing the generation of EPO and IL-1 has the ability to reduce erythropoiesis [52]. The precursors decrease the expression of the EPO receptor, hence impeding the generation of EPO [53]. Furthermore, IL-1 and other proinflammatory cytokines have been linked to the activation of macrophages for erythrophagocytosis, which causes the early erythrocyte destruction and reduced erythrocyte survival [54].

Also, IL-1 has a role in a number of modifications to nutritional status and energy metabolism, by activating its effects inside the hypothalamic nuclei central nervous system, IL-1 causes anorexia linked to decreased food intake [55].

As a result, growth hormone (GH) is inhibited, which lowers the synthesis of insulin-like growth factor-1 that causes the loss of muscle mass that is common in individuals with advanced cancer [56]. Furthermore, IL-1 prevents pancreatic beta cells from producing insulin, which results in hyperinsulinemia and insulin resistance [57]. The emergence of cancer related anemia (CRA) in individuals with advanced cancer may be associated with these IL-1-mediated actions [58]. Erythropoiesis is specifically harmed by low glucose availability and insulin resistance because glucose metabolism is the only factor that al-

lows commitment to the differentiation phases [59]. Cellular absorption of glucose and its incorporation into the tricarboxylic acid cycle are crucial for erythroid development since they provide a substantial amount of energy required for cell proliferation [60]. Additionally, there is an increased redirection of glucose towards the pentose phosphate pathway to generate carbon sugars and facilitate glutamine-dependent nucleotide synthesis [61].

Erythroid differentiation is affected by the intake of glucose and the balance among mitochondrial and non-mitochondrial glucose metabolism [62]. Furthermore, there is proof that anemia and the central nerves system (CNS) pathways regulated by IL-1 are related. Research has demonstrated a correlation between the replacement of GH and a notable increase in Hemoglobin (Hb) [63].

Moreover, results from in vitro and in vivo investigations shown that Insulin-like growth factor 1 (IGF-1) has the ability to enhance the differentiation and proliferation of both early and late erythroid progenitors [64]. clinical investigations have consistently shown that blood levels of IGF-1 are inversely correlated with hemoglobin in a variety of demographics, including adult, elderly, and dialyzed patients [65].

TNF-a has a direct impact on hemopoiesis. It may impede the production of red blood cells and their maturation, both in living organisms and in laboratory settings. Additionally, it can raise the mortality rate of immature red blood cells and reduce the quantity of mature red blood cells. Furthermore, it diminishes the responsiveness of erythroid progenitor cells to EPO [66]. Moreover, TNF-a primarily contributes to the metabolic changes in lipid metabolism that often occur in individuals with advanced cancer, particularly those experiencing cachexia [67].

Additionally, it has also been shown that regulates the development of erythroid progenitors [68]. Regarding IL-6, it affects erythropoiesis at several levels by modifying hepatic gene expression and hepcidin production, IL-6 can alter iron metabolism and limit erythroid progenitors' ability to proliferate and respond to EPO, this, in turn, causes the functional iron shortage that is characteristic of CRA [10].

Research has demonstrated that IL-6 can impact erythropoiesis by inhibiting the synthesis of hemoglobin. This effect occurs separately from the hepcidin-iron pathway and is a result of the declining mitochondrial function in maturing erythroid cells, which leads to a decrease in membrane potential or oxidative phosphorylation [69]. Numerous publications have shown the critical role that IL-6 plays in CRA determination, one of our articles gave the first evidence that IL-6, in conjunction with the stage of the illness, acted as an autonomous predictor of Hb levels in a group of ovarian cancer patients [50].

Furthermore, IL-6 significantly contributes to the pathogenesis of chronic renal failure (CRA) as well as the profound immunological and metabolic alterations that characterize advanced illness. In a previous endeavor, an animal model was used in order to simulate cancer-related situations for experimental purposes [70]. It was demonstrated that IL-6 played a critical role in causing the early start of cachexia symptoms, which were linked to the loss of muscle and adipose tissues in addition to a decrease in appetite and were independent of the rate of tumor growth. The amount of IL-6 was directly correlated with the degree of cachexia, and a notable decrease in IL-6 levels occurred after the original tumor was removed. Anti-IL-6 monoclonal antibodies consistently delayed the onset of cachexia symptoms [70].

Additionally, studies conducted on rat experimental models have shown that IL-6, similar to IL-1, directly stimulates the hypothalamus to initiate the secretion of CRF, a process that is facilitated by Prostaglandin E2 (PGE2) [71]. It may affect the pancreatic b cells' ability to produce insulin and metabolize food [72]. In more recent times, IL-6 has come to light as the primary factor influencing muscle atrophy in patients with advanced cancers [73]. Currently, there is a significant emphasis on regulating the, phosphatidylinositol-3-kinase(PI3K), protein kinase B (AKT), mammalian target of rapamycin (mTOR) pathway this system serves as the main detector of cellular energy and is responsible for stimulating muscle development. IL-6 and signal transducer and activator of transcription 3 (STAT3) have been identified as key factors in this control [74].

Patients with advanced cancer may have impaired production of red blood cells due to the activation of certain pathways controlled by IL-6, as well as the accelerated breakdown and restricted supply of amino acids associated with this condition. Increased amino acid intake stimulates mammalian target of rapamycin (mTOR) signaling, which subsequently promotes the development of red blood cells and the manufacture of hemoglobin [75]. On the other hand, decreased nutrient and amino acid pools result in decreased mTOR activity and suppressed Hb production [76].

Insulin resistance, which results in poor glucose metabolism, and anorexia, which is linked to decrease

food intake, both contribute to the mTOR pathway's suppression. Consequently, mTORC1 signaling may be inhibited by anemia, which is characterized by a less effective transport of oxygen (O2) to peripheral tissues. This is mostly due to lower adenosine triphosphate (ATP) production and poor oxidative phosphorylation, which result in mTOR suppression. Additionally, "functional iron deficiency," which is characterized by low iron levels and subsequently low heme production a key component of muscle myoglobin distinguishes CRA this implies that muscular atrophy is exacerbated by anemia [73].

3. Erythropoiesis

Several physiological processes that can also alter in response to various pathological circumstances can control the rate of new cell production [77]. Delivery of oxygen from the lungs to various body locations and carbon dioxide in the opposite direction is primarily the function of erythrocytes [78].

A stable and suitable erythrocyte mass must be maintained, but it must also be able to expand in response to tissue hypoxia, given that the body's capacity to store oxygen is 20 mL/kg and its basal oxygen used is 4 mL/kg/min [79]. In actuality, hypoxia-inducible factor (HIF)-1 stimulates erythropoietin synthesis at the molecular level during hypoxia [80]. Furthermore, vascular endothelial growth factor (VEGF) and many other growth factors are used to counterbalance the detrimental consequences of low oxygen levels [81]. As a result, the inverse relationship between the value of Hb or hematocrit and the rise in EPO levels is log-linear [52].

There is a significant correlation between energy metabolism and the availability of oxygen, since oxygen transported by hemoglobin is essential for glucose metabolism and the production of energy [82]. Conversely, protoporphyrin IX (PPIX), which is produced as a result of glucose metabolism via the Krebs cycle, is used to form the heme molecule, which serves as the cellular carrier of oxygen [83]. While hemoglobin (Hb) is essential for carrying oxygen (O2), glucose is required for the production of heme, which in turn is necessary for the synthesis of Hb. The crucial role of diet is seen in the need of iron and glucose for heme synthesis explain in Figure 4 [84].

The four primary processes that govern erythropoiesis are as follows: (1) The capacity for proliferation of the reserve of erythroid progenitors; (2) The strength of the stimuli for the creation of erythrocytes; (3) The availability of nutrients; and (4) The survival of erythrocytes, which is reduced during bleeding or due to early destruction [85].

4. Prevalence of Anemia in Cancer Patients

According to a major prospective survey from the European Cancer Anemia Survey (ECAS) with 15367 cases showed that the prevalence of anemia was 39.3% at enrollment and 67.0% during the survey [86]. Anemia prevalence at diagnosis was 18.98% in the Chinese population, according to our previous investigation of 1133 newly diagnosed cancer patients. Other factors such as age, reduced food intake, and a history of bleeding were also found to be independent risk factors for the development of anemia at the time of diagnosis in this cohort [87]. However, the incidence is significantly more common in those undergoing radiation or chemotherapy [88]. Cytotoxic chemotherapy is believed to be a primary factor contributing to anemia in cancer patients, the severity of anemia is determined by the extent of the malignancy and the dosage of treatment administered [89].

5. Sign and Symptom of Anemia and Quality of Life

The severity of symptoms can range from mild conditions like palpitations, dizziness, dyspnea, anorexia, and trouble concentrating to more serious ones like heart failure and lethargy [90].Vital symptoms that cancer patients experience is fatigue, which can hurt the patient's quality of life [91].

Depending of previous study show that the 78% of 419 cancer patients who were chosen at random to participate in a study stated they had become fatigued while undergoing treatment or dealing with their illness. Furthermore, more than cancer-related discomfort, 61% of the patients said that exhaustion hurt their lives [92]. Although anemia is thought to be a major contributing factor, cancer fatigue has diverse pathogenesis processes [93].

6. Anemia as an adverse prognostic factor

Anemia has been shown in several studies to be an autonomous risk factor for reduced survival in cancer patients, especially those undergoing both chemotherapy and radiation therapy. Furthermore, it significantly affects their quality of life [94].

There are conflicting reports, nevertheless, about increased survival after anemia correction conducted a relatively old investigation in which they examined sixty published publications describing cancer patients' survival based on their hemoglobin level

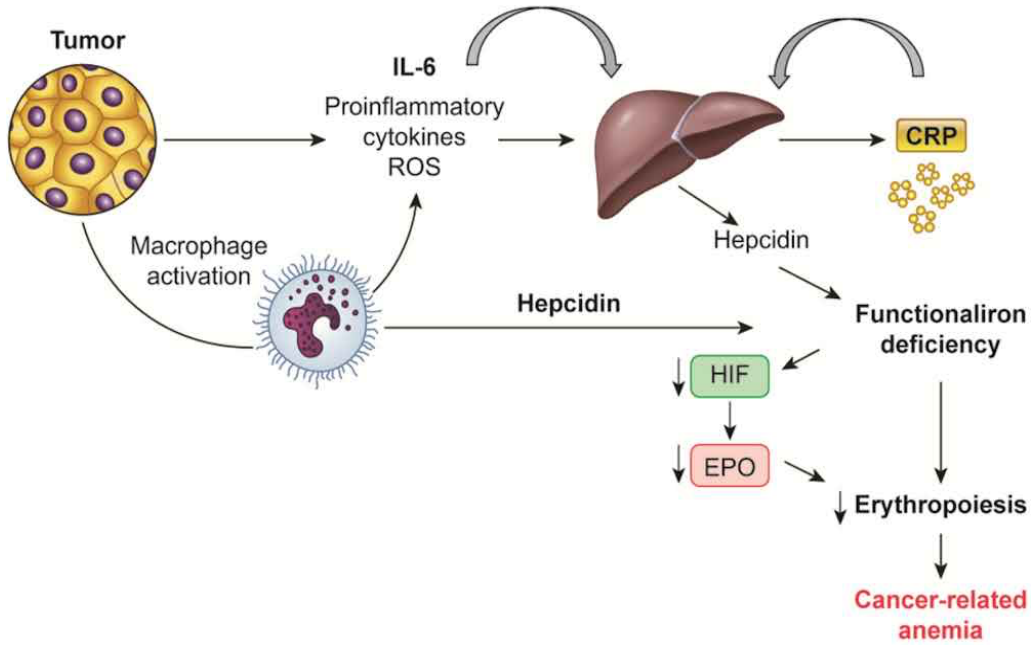

Figure 4. Pathogenesis of chemotherapy-induced anemia with erythropoiesis [135]

[95]. Anemia increased the total comparative risk of mortality in this diverse group of cancer patients by 19% in lung cancer patients, 47% in prostate cancer patients, 67% in lymphoma patients, and 75% in head and neck cancer patients [94].

7. Anemia Pathogenesis in Cancer Patients

Anemia may develop in patients with malignant illnesses for a variety of causes. The most common kind of anemia that patients with solid tumors have been known as "anemia of chronic disease" [96]. This condition has been seen in severe infections, trauma, chronic inflammatory disorders, and cancer [97]. In addition to hyperferritinemia and elevated iron storage, associated test findings include hypoferraemia and reduced transferrin saturation [98]. It is believed that the release of cytokines linked to chronic illness, IL-1, TNF and interferon beta, mediates this type of anemia [99]. These cytokines may result in decreased iron utilization, a reduction in colony-forming activity (BFU-E), and a shorter lifetime for red blood cells. An apparent low amount of EPO is commonly noted about the severity of anemia in these individuals [100-102]. These modifications result in an overall reduced RBC synthesis in the bone marrow, which is the most likely pertinent pathway for cancer-related anemia [103].

Factors contributing to the development of anemia in cancer patients

- Hemolysis
- Bleeding
- Hypersplenism, haemophagocytosis
- Nutritional deficiencies
- Chemotherapy, radiotherapy
- Anemia of chronic disorders
- Marrow damage
- Renal insufficiency)

Enumeration of distinct etiologies of therapy-induced anemia specifically associated with certain therapeutic interventions. [103]

- Radiotherapy
- Chemotherapy (depending on the drug, schedule, and dose)
- Combined radio-chemotherapy
- Surgery

List of related to underlying anemia of chronic disease[103]

- Reduced iron utilization
- Relative EPO deficiency
- Reduced RBC survival

8. Treatment of Anemia in Cancer Patient

Anemia's etiology should be determined, and treatment should focus on addressing the underlying cause. Directed therapy intervention may not work, though; pinpointing a precise causative component can occasionally be challenging. The therapeutic options represent in Table 2. Therapeutic Interventions in CIA [128]. That will be covered in the upcoming

Table 2. Therapeutic Interventions in CIA [128]

Therapy	Indications	Advantages	Disadvantages
RBC Transfusion	• Symptomatic CIA • Consider when Hb <8 g/dL • Consider comorbidities • Single-unit transfusion policy with administration of one unit at a time titrated to symptom resolution	•Rapid hemoglobin improvement •Rapid improvement in anemia symptoms • Enhance overall quality of life	• Pathogen transmission • Transfusion reaction • Alloimmunization • Increased thrombotic risk • May impact disease progression • Iron overload • Increased thrombotic risk • Seizures • Slow to improve hemoglobin
ESA administration	• Symptomatic CIA • Consider when Hb ≤10 g/dL	• Reduce RBC requirements • Diminished severity and duration of CIA • Improve quality of life	• Hypertension • Nausea, vomiting, diarrhea • Headache • Pruritus • Slow to improve hemoglobin
Intravenous iron supplementation	• Absolute iron deficiency (TSAT <20%, ferritin <30 ng/mL)7 • Functional iron deficiency (TSAT <50%, ferritin 30–500 ng/mL)7 • Consider when Hb ≤11 or has decreased by ≥2 g/dL from baseline level ≥12 g/dL in the setting of absolute iron deficiency as defined by serum ferritin <100 ng/mL29 • Consider before ESA administration	•Reduces RBC requirements • Facilitates optimal ESA response	• Hypertension • Dizziness • Dyspnea

Legend: RBC: Red Blood Cell, CIA: Cancer induced anemia, Hb: Hemoglobin, TSAT: Transferrin saturation, ESAs: Erythropoietin stimulating agents.

sections include intravenous (IV) iron therapy, erythropoietin-stimulating medications, and blood transfusions [30].

The United States Food and Drug Administration has authorized two erythropoiesis-stimulating medicines for the treatment of chemotherapy-induced anemia [40]. The Food and Drug Administration (FDA) has authorized the use of erythropoietin at a dosage of 40,000 Units (U) each week or 150 U per kg three times per week for patients with chemotherapy-induced anemia and hemoglobin levels below 10 g/dL [104]. Additionally, darbepoetin Alfa Dimensional Assessment of Repetitive Behavior (DARB) may be administered at a dosage of 500 micrograms (mcg) every three weeks or 2.25 mcg per kg weekly, empirical studies have shown that both EPO and DARB had equivalent efficacy in reducing the need for blood transfusions in individuals with chemotherapy-induced anemia [41].

8.1 Iron Supplementation

Erythropoietin deficiency and improper iron absorption into growing erythrocytes are two characteristics of anemia linked to cancer. Consequently, it has been suggested that CRA may be treated with an iron supplement and ESA combination. Depending on the severity and timing of cancer-associated anemia, the oral or IV method of iron replacement is selected. Oral and parenteral iron formulations (low-molecular-weight iron dextran, ferric gluconate, and iron sucrose) are evaluated in cancer patients. The addition of iron to ESAs versus ESAs alone for chemotherapy-induced anemia has been linked to improved Hb alterations, fewer RBC transfusions, and a higher hematological response, according to a recent systematic meta-analysis. In contrast to ESAs alone, the meta-analysis did not demonstrate any improvement reduction in time to hematological response in patients supplemented with iron. There have been no documented treatment-related fatalities [105]. There are two different ways to administer iron: intravenously or orally. Oral iron in the bivalent (ferrous) form is

Table 3. Laboratory Tests Used To Evaluate Iron Status [137]

Test	Normal Range
Serum Ferritin	Male 30-500 ng/mL Female 12-240 ng/mL
Serum Total Iron	Male 50-170 mg/dL Female 30-160 mg/dL
TIBC	240-450 mg/dL
TSAT	20%-50%
ZPP	<70 mmol/mol heme
STfR	Male 2.2-5.0 mg/L Female 1.9-4.4 mg/L
Hepcidin	<64.3 ng/Ml
Reticulocyte Count	0.5% – 2.5%
MCV	Male 83-98 fL Female 85-98 fL

Legend: TIBC: Total iron Binding Capacity, TSAT: Transferrin saturation, ZPP: Zinc protoporphyrin, STfR: Soluble transferrin receptor, MCV: Mean corpuscular volume, ng/mL: nanograms per milliliter, mg/dL: milligrams per deciliter. FL: Femtoliter.

more bioavailable than the trivalent (ferric) form. Ferrous gluconate is less dangerous than iron dextran in terms of safety [106, 107].

Parenteral iron toleration is linked to several side effects, including headache, dizziness, discomfort, hypertension, nausea, vomiting, and/or diarrhea. The majority of adverse events reported in the literature were linked to the use of high molecular weight iron dextran, which is no longer advised and is now substituted by other formulations in clinical practice [108]. Significantly, recent findings in individuals without ongoing cancer indicate that thrombocytosis associated with iron deficiency anemia may raise the risk of thrombosis by about two times when compared to individuals with IDA alone.

Oral iron is less expensive, however, there is conflicting evidence about its efficacy in treating anemia of inflammation [91, 109]. In two prospective trials, the superiority of IV iron over oral iron for improving Hb was not demonstrated in individuals with cancer-associated anemia [109, 110]. Some laboratory test need to all patient with chemotherapy induced anemia to evaluate the degree of anemia and detect amount each molecular such as iron and ferritin to see in detail in Hata! Başvuru kaynağı bulunamadı.

The primary iron regulator and frequent cause of iron homeostasis problems in cancer patients is hepcidin, an acute phase reactant generated in a setting of inflammation [111]. Patients with renal insufficiency may have even higher levels of hepcidin, impairing their ability to absorb iron through the mouth [112, 113]. Intravenous iron and are not constrained by a disturbed absorption system in an inflammatory environment, in contrast to the oral version, which is restricted by hepcidin [112, 114].

When a patient has an absolute iron shortage, as evidenced by a serum ferritin level of less than 100 ng/mL, intravenous iron is suggested in cases of CIA in patients with a hemoglobin level of less than 11 or a reduction in hemoglobin of at least 2 g/dL from a baseline level of at least 12 g/dL [115].

8.2 Erythropoietin

The hormone erythropoietin a circulatory hematopoietic glycoprotein, was first discovered in 1906 and aids in the synthesis of red blood cells [116]. EPO is expressed by the interstitial cells of the liver and kidneys, and it is increased in hypoxic environments to promote the synthesis of red blood cells in the bone marrow [116, 117]. EPO attaches to erythroid precursor cells to enhance both maturation and differentiation after being secreted by the liver and kidneys [116]. ESAs are a type of recombinant drugs that use iron stores required for healthy erythropoiesis to promote red cell growth[118].

Anemia was a common side effect of chemotherapy and cancer in the early 1980s, and red blood cell transfusion was the recommended course of treatment. Historically, doctors would sometimes transfuse patients based only on their symptoms, with the transfusion threshold being approximately 8 g/dL. In the latter part of the 1980s, Amgen successfully cloned epoetin alfa, and in the early 1990s, the CIA approved darbepoetin alfa, a molecule containing additional sugar moieties. When compared to a placebo, epoetin alfa and darbepoetin alfa has both been demonstrated

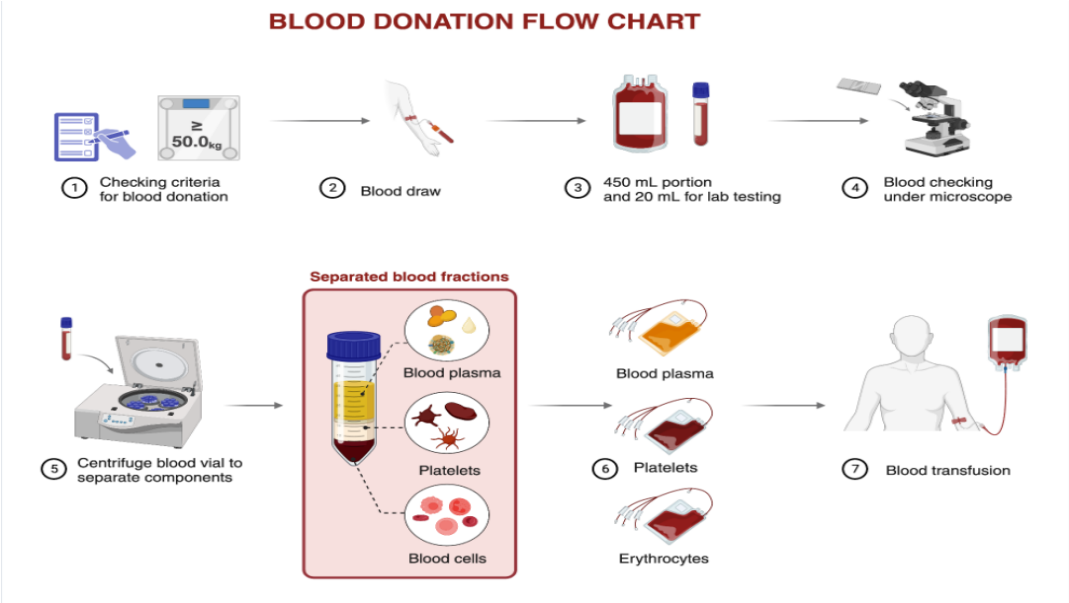

Figure 5. process of blood transfusion [136]

to improve quality of life [119, 120] . Human immunodeficiency virus(HIV), CIA, and end-stage renal disease are just a few of the illnesses that have shown that increased quality of life is correlated with higher hemoglobin levels [111, 121].

One of the main objectives of using ESAs in CIA is to reduce the requirement for RBC transfusions while simultaneously improving QOL and achieving sustained anemia correction [31]. Following the US food and drug administration's approval of darbepoetin and epoetin for use by the CIA [122]. Numerous randomized clinical trials have demonstrated that ESA improved Hb levels and decreased the need for RBC transfusions in patients with CIA [94].

8.3 Red Blood Cell Transfusion

Therefore, optimal blood transfusion shows Figure 5 in depends on the grade of anemia and hemoglobin concentration level [123, 124]. Notably, improved oxygen delivery is not achieved by transfusion of red blood cells to hemoglobin levels higher than 7 g/dL [1]. While transfusions of red blood cells can quickly increase hemoglobin, Provide a brief description of the content of the Table 4 and amount of increasing of blood after blood transfusion are 1%-3% of transfusions are associated with unfavorable outcomes [124].

A few of these side effects include hemolysis of incompatible plasma or red blood cells, allergic reaction, immunologic compromise, thrombosis, infections, acute lung injury associated with transfusions, and the development of antibodies against the human leukocyte antigen [115, 125].

Red blood cell transfusions may interact negatively with chemotherapy in addition to the concerns already discussed [126]. Blood can be kept in storage for up to 42 days after donation, but the longer it is kept, the quality of this blood can be lower, extended blood storage is linked to modifications in the metabolism, morphology, and rheology of red blood cells the loss of proteins, lipids, and carbohydrates from the membrane and changes in secretion, adhesion, and oxygen delivery [127, 128]. Acute lung injury linked with transfusion is the second most common blood transfusion complication, after delayed hemolytic response. However, donor leukocytes in the transfusion are primarily responsible for the majority of immunologic and viral issues brought on by blood transfusions. Leukocytes are the vector used by blood transfusion-transmitted viruses to infect their host, the most prevalent being hepatitis B. Hepatitis C, HIV, hepatitis A virus, cytomegalovirus (CMV), Epstein-Barr virus, human herpes virus 8, toxoplasma, parvovirus B-19, West Nile virus, spongiform encephalopathy prions, Chagas, Babesia, and malaria are among the other viruses that are less likely to be spread [129].

9. Treatment of Cancer induced anemia

It is possible to discover highly cytotoxic pharmacologic regimens and assess the effects of chemotherapy-induced myelosuppression by developing screening tests that use hematopoietic stem progenitor from peripheral blood and bone marrow [130]. Different

Table 4. Organization and recommendations for red blood cell transfusion [128]

Organization	Recommendations
AABB [128]	• Maintain hemoglobin ≥7 g/dL in hemodynamically stable hospitalized patients • Consider transfusion in patients with hemoglobin ≤8 g/dL and preexisting cardiovascular disease • Personalize all transfusions by both symptoms and hemoglobin levels
ESMO [115] (2018)	• Recommend transfusion in patients with hemoglobin level <7–8 g/dL and/or with severe anemia-related symptoms, regardless of hemoglobin level
NCCN [28] (2018)	• Recommend transfusion of patients with symptomatic anemia • Monitor and reevaluate patients with asymptomatic anemia who lack significant comorbidities • Consider transfusion in patients who are at high risk with progressive hemoglobin decline in the setting of recent chemo radiation or asymptomatic with comorbidities such as cardiopulmonary or cerebrovascular disease

Legend: (AABB) American Association of Blood Banks, (ESMO) European Society of Medical Oncology, (NCCN) National Comprehensive Cancer Network, (g/dL) Grams per Deciliter.

hormones and pharmaceutical agents have an impact on the management and prevention of CIA in addition to new screening methods. Myelosuppression of neoplastic cells may be selectively induced by tyrosine kinase inhibitors when administered after chemotherapy, but not of bone marrow progenitor cells [131]. Arginine vasopressin, transforming growth factor beta inhibitors, eryptosis inhibitors, and medications that block the HIF-1α pathway may support and maintain erythropoiesis while also shielding renal tubular and endothelial cells [132-134]. Researchers are looking into using roxadustat, a reversible HIF prolyl hydroxylase inhibitor, to lessen the need for red blood cell transfusions. Roxadustat boosts the expression of both erythropoietin and related receptors, there is hope that CIA prevention, early detection, and timely treatment will result in fewer dosage delays, fewer dose reductions, and better patient outcomes.

CONCLUSION

The prevalence of anemia in adult cancer patients undergoing chemotherapy is influenced by various factors associated with chemotherapy-induced anemia, including the cancer grade, degree of anemia, duration of malignancy presentation, and treatment intensity. The exact etiology of chemotherapy-induced anemia remains incompletely understood, although some theories suggest mechanisms that hasten the development of anemia. For instance, many commonly used chemotherapeutic agent's impact the cell cycle, leading to a slowdown in the division of normal cells. Hence, chemotherapy affects not only cancer cells but also normal cells, impeding their division. The most effective treatments for anemia in cancer patients include erythropoietin-stimulating agents, red blood cell transfusions, and iron supplementation, each with its own set of advantages and disadvantages detailed in previous literature. For future research endeavors, it is recommended that investigators focus on identifying the safest approach to managing anemia in cancer patients, one that minimizes adverse side effects.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1.Radziwon P, Krzakowski M, Kalinka E, Zaucha R, Wysocki P, Kowalski D, Gryglewicz J, Wojtukiewicz MZ. Anemia in cancer patients—Expert Group recommendations. Revision 2020. Hematology in Clinical Practice. 2020;11(1):1-11.

2.Van Belle SJ-P, Cocquyt V. Impact of haemoglobin levels on the outcome of cancers treated with chemotherapy. Critical reviews in oncology/hematology. 2003;47(1):1-11.

3.Gilreath JA, Stenehjem DD, Rodgers GM. Diagnosis and treatment of cancer-related anemia. American journal of hematology. 2014;89(2):203-12.

4.Langer CJ, Choy H, Glaspy JA, Colowick A. Standards of care for anemia management in oncology: focus on lung carcinoma. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2002;95(3):613-23.

5.Kano Y, Kajiwara K, Kozai YJTAJotMS. Cancer-related Microangiopathic Hemolytic Anemia2023;365(2):e15-e6.

6.Xu J, Wu K, Li X, Teo CS, Li G, Pan Y, Hou LJJoTCMS. Effectiveness and safety of seven oral Chinese patent medicines as adjuvant therapy for cancer-related anemia: A systematic

review and network meta-analysis of randomized controlled trials2023.
7.Gilreath JA, Rodgers GMJB, The Journal of the American Society of Hematology. How I treat cancer-associated anemia2020;136(7):801-13.
8.Hess G, Nordyke RJ, Hill J, Hulnick S. Effect of reimbursement changes on erythropoiesis-stimulating agent utilization and transfusions. American journal of hematology. 2010;85(11):838-43.
9.Steensma DP. Is anemia of cancer different from chemotherapy-induced anemia? Journal of Clinical Oncology. 2008;26(7):1022-4.
10.Adamson JW. The anemia of inflammation/malignancy: mechanisms and management. ASH Education Program Book. 2008;2008(1):159-65.
11.Foundation NK. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2006;47(5 Suppl 3):S11-S145.
12.Анемії K. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney international. 2012;2:279.
13.Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. Journal of the National Cancer Institute. 1999;91(19):1616-34.
14.Jefferies S, Rajan B, Ashley S, Traish D, Brada M. Haematological toxicity of cranio-spinal irradiation. Radiotherapy and oncology. 1998;48(1):23-7.
15.Dessypris E. The biology of pure red cell aplasia. Semin Hematol. 1991;28:275-84.
16.Wang SA, Yue G, Hutchinson L, Landry ML, Hasserjian RP, Hao S, Galili N, Raza A, Woda BA. Myelodysplastic syndrome with pure red cell aplasia shows characteristic clinicopathological features and clonal T-cell expansion. British journal of haematology. 2007;138(2):271-5.
17.Cheng Z, Yan M, Lu Y, Pan X-TJH. Expression of serum BMP6 and hepcidin in cancer-related anemia2020;25(1):134-8.
18.Muthanna FM, Samad A, Ibrahim HK, Al-Awkally N-AM, Sabir SJIJoHS. Cancer related anaemia (CRA): An overview of approach and treatment2022(II):2552-8.
19.Gordon M, Kearney L, Hibbin J. Effects of human marrow stromal cells on proliferation by human granulocytic (GM-CFC), erythroid (BFU-E) and mixed (Mix-CFC) colony-forming cells. British Journal of Haematology. 1983;53(2):317-25.
20.Kobune M, Kawano Y, Kato J, Ito Y, Chiba H, Nakamura K, Fujimi A, Matsunaga T, Hamada H, Niitsu Y. Expansion of CD34+ cells on telomerized human stromal cells without losing erythroid-differentiation potential in a serum-free condition. International journal of hematology. 2005;81:18-25.
21.Werner TL, Agarwal N, Carney HM, Rodgers GM. Management of cancer-associated thrombotic microangiopathy: What is the right approach? American journal of hematology. 2007;82(4):295-8.
22.Madeddu C, Neri M, Sanna E, Oppi S, Macciò AJJoEP. Experimental drugs for chemotherapy-and cancer-related anemia2021:593-611.
23.Abiri B, Vafa MJN, cancer. Iron deficiency and anemia in cancer patients: the role of iron treatment in anemic cancer patients2020;72(5):864-72.
24.Abdel-Razeq H, Hashem HJCrioh. Recent update in the pathogenesis and treatment of chemotherapy and cancer induced anemia2020;145:102837.
25.Chant C, Wilson G, Friedrich JO. Anemia, transfusion, and phlebotomy practices in critically ill patients with prolonged ICU length of stay: a cohort study. Critical care. 2006;10:1-9.
26.Amato A, Pescatori M. Perioperative blood transfusions and recurrence of colorectal cancer. Cochrane database of systematic reviews. 2006(1).
27.Kirshner J, Hatch M, Hennessy DD, Fridman M, Tannous RE. Anemia in stage II and III breast cancer patients treated with adjuvant doxorubicin and cyclophosphamide chemotherapy. The oncologist. 2004;9(1):25-32.
28.Rodgers GM, Becker PS, Blinder M, Cella D, Chanan-Khan A, Cleeland C, Coccia PF, Djulbegovic B, Gilreath JA, Kraut EH. Cancer-and chemotherapy-induced anemia. Journal of the National Comprehensive Cancer Network. 2012;10(5):628-53.
29.Grotto H. Anaemia of cancer: an overview of mechanisms involved in its pathogenesis. Medical oncology. 2008;25:12-21.
30.Natalucci V, Virgili E, Calcagnoli F, Valli G, Agostini D, Zeppa SD, Barbieri E, Emili RJN. Cancer related anemia: an integrated multitarget approach and lifestyle interventions2021;13(2):482.
31.Aapro MS. Anemia Management with Erythropoiesis-Stimulating Agents: A Risk–Benefit Update. Oxford University Press; 2008. p. 1-3.
32.Al-Refaie WB, Parsons HM, Markin A, Abrams J, Habermann EB. Blood transfusion and cancer surgery outcomes: a continued reason for concern. Surgery. 2012;152(3):344-54.
33.Arezes J, Jung G, Gabayan V, Valore E, Ruchala P, Gulig PA, Ganz T, Nemeth E, Bulut Y. Hepcidin-induced hypoferremia is a critical host defense mechanism against the siderophilic bacterium Vibrio vulnificus. Cell host & microbe. 2015;17(1):47-57.
34.Abdel-Razeq HN. Cancer-related anemia. Saudi medical journal. 2004;25(1):15-20.
35.Ramli NA, Iberahim S, Ismail AAC, Hussin HJCJoIM. Incidence of anemia and red blood cell (RBC) transfusion requirement in breast cancer2023;14(2):237.
36.Abdel-Razeq H, Hashem H. Recent update in the pathogenesis and treatment of chemotherapy and cancer induced anemia. Critical reviews in oncology/hematology. 2020;145:102837.
37.Cosse J-P, Michiels C. Tumour hypoxia affects the responsiveness of cancer cells to chemotherapy and promotes cancer progression. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents). 2008;8(7):790-7.
38.Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M. World Alzheimer report 2015. The global impact of dementia: an analysis of prevalence, incidence, cost and trends: Alzheimer's disease international; 2015.
39.Höckel M, Vaupel P, editors. Biological consequences of tumor hypoxia. Seminars in oncology; 2001: Elsevier.
40.Family L, Xu L, Xu H, Cannavale K, Sattayapiwat O, Page JH, Bohac C, Chao CJSCiC. The effect of chemotherapy-induced anemia on dose reduction and dose delay2016;24:4263-71.
41.Vaupel P, Mayer A. Hypoxia in cancer: significance and impact on clinical outcome. Cancer and Metastasis Reviews. 2007;26:225-39.
42.Macciò A, Madeddu C. Inflammation and ovarian cancer. Cytokine. 2012;58(2):133-47.
43.Sharma A, Jasrotia S, Kumar AJN-SsAoP. Effects of Chemotherapy on the Immune System: Implications for Cancer Treatment and Patient Outcomes2023:1-16.

44.Betts KA, Gao S, Ray S, Schoenfeld AJJFO. Real-world safety of first-line immuno-oncology combination therapies for advanced non-small-cell lung cancer2024(0).
45.Delano MJ, Moldawer LL. The origins of cachexia in acute and chronic inflammatory diseases. Nutrition in clinical practice. 2006;21(1):68-81.
46.Wang J, Li L, Xu ZPJSM. Enhancing Cancer Chemo-Immunotherapy: Innovative Approaches for Overcoming Immunosuppression by Functional Nanomaterials2023:2301005.
47.Elena M-B, Jean-Hugues G, Belen P-OA, Christophe LJBR. Beyond current treatment of Fanconi Anemia: What do advances in cell and gene-based approaches offer?2023:101094.
48.Ladányi A, Somlai Bt, Gilde K, Fejös Z, Gaudi I, Tímár Jz. T-cell activation marker expression on tumor-infiltrating lymphocytes as prognostic factor in cutaneous malignant melanoma. Clinical Cancer Research. 2004;10(2):521-30.
49.Macciò A, Lai P, Santona MC, Pagliara L, Melis GB, Mantovani G. High serum levels of soluble IL-2 receptor, cytokines, and C reactive protein correlate with impairment of T cell response in patients with advanced epithelial ovarian cancer. Gynecologic oncology. 1998;69(3):248-52.
50.Maccio A, Madeddu C, Massa D, Mudu MC, Lusso MR, Gramignano G, Serpe R, Melis GB, Mantovani G. Hemoglobin levels correlate with interleukin-6 levels in patients with advanced untreated epithelial ovarian cancer: role of inflammation in cancer-related anemia. Blood. 2005;106(1):362-7.
51.Macciò A, Madeddu C, Massa D, Astara G, Farci D, Melis GB, Mantovani G. Interleukin-6 and leptin as markers of energy metabolicchanges in advanced ovarian cancer patients. Journal of Cellular and Molecular Medicine. 2009;13(9b):3951-9.
52.Spivak JL. The anaemia of cancer: death by a thousand cuts. Nature Reviews Cancer. 2005;5(7):543-55.
53.Faquin WC, Schneider TJ, Goldberg MA. Effect of inflammatory cytokines on hypoxia-induced erythropoietin production1992.
54.Aboderin FI, Oduola T, Davison GM, Oguntibeju OOJB. A Review of the Relationship between the Immune Response, Inflammation, Oxidative Stress, and the Pathogenesis of Sickle Cell Anaemia2023;11(9):2413.
55.Yuan T, Jia Q, Zhu B, Chen D, Long HJCC, Signaling. Synergistic immunotherapy targeting cancer-associated anemia: prospects of a combination strategy2023;21(1):117.
56.Saini A, Nasser A-S, Stewart CE. Waste management—cytokines, growth factors and cachexia. Cytokine & growth factor reviews. 2006;17(6):475-86.
57.Burke SJ, Stadler K, Lu D, Gleason E, Han A, Donohoe DR, Rogers RC, Hermann GE, Karlstad MD, Collier JJ. IL-1β reciprocally regulates chemokine and insulin secretion in pancreatic β-cells via NF-κB. American journal of physiology-endocrinology and metabolism. 2015;309(8):E715-E26.
58.Al-Samkari H, Kessler CM, Auerbach MJh. Recognition of thrombotic risk of thrombocytosis in iron deficiency2021;106(3):661.
59.Oburoglu L, Romano M, Taylor N, Kinet S. Metabolic regulation of hematopoietic stem cell commitment and erythroid differentiation. Current Opinion in Hematology. 2016;23(3):198-205.
60.Koppenol WH, Bounds PL. The Warburg effect and metabolic efficiency: re-crunching the numbers. Science. 2009;324(5930):1029-33.
61.Montel-Hagen A, Sitbon M, Taylor N. Erythroid glucose transporters. Current opinion in hematology. 2009;16(3):165-72.
62.Oburoglu L, Tardito S, Fritz V, De Barros SC, Merida P, Craveiro M, Mamede J, Cretenet G, Mongellaz C, An X. Glucose and glutamine metabolism regulate human hematopoietic stem cell lineage specification. Cell stem cell. 2014;15(2):169-84.
63.Christ E, Cummings M, Westwood N, Sawyer B, Pearson T, Sonksen P, Russell-Jones D. The importance of growth hormone in the regulation of erythropoiesis, red cell mass, and plasma volume in adults with growth hormone deficiency. The Journal of Clinical Endocrinology & Metabolism. 1997;82(9):2985-90.
64.Jameus A, Kennedy AE, Thome CJD-R. Hematological changes following low dose radiation therapy and comparison to current standard of care cancer treatments2021;19(4):15593258211056196.
65.Iglesias P, Diez JJ, Fernandez-Reyes MJ, Aguilera A, Burgués S, Martinez-Ara J, Miguel JL, Gómez-Pan A, Selgas R. Recombinant human growth hormone therapy in malnourished dialysis patients: a randomized controlled study. American journal of kidney diseases. 1998;32(3):454-63.
66.Buck I, Morceau F, Grigorakaki C, Dicato M, Diederich M. Linking anemia to inflammation and cancer: the crucial role of TNFα. Biochemical pharmacology. 2009;77(10):1572-9.
67.Patel HJ, Patel BM. TNF-α and cancer cachexia: Molecular insights and clinical implications. Life sciences. 2017;170:56-63.
68.Nagasawa E, Abe Y, Nishimura J, Yanase T, Nawata H, Muta K. Pivotal role of peroxisome proliferator–activated receptor γ (PPARγ) in regulation of erythroid progenitor cell proliferation and differentiation. Experimental hematology. 2005;33(8):857-64.
69.McCranor BJ, Kim MJ, Cruz NM, Xue Q-L, Berger AE, Walston JD, Civin CI, Roy CN. Interleukin-6 directly impairs the erythroid development of human TF-1 erythroleukemic cells. Blood Cells, Molecules, and Diseases. 2014;52(2-3):126-33.
70.Strassmann G, Fong M, Kenney J, Jacob C. Evidence for the involvement of interleukin 6 in experimental cancer cachexia. The Journal of clinical investigation. 1992;89(5):1681-4.
71.Turnbull AV, Lee S, Rivier C. Mechanisms of Hypothalamic-Pituitary-Adrenal Axis Stimulation by Immune Signals in the Adult Rat a. Annals of the New York Academy of Sciences. 1998;840(1):434-43.
72.SANDLER S, BENDTZEN K, Eizirik DL, WELSH M. Interleukin-6 affects insulin secretion and glucose metabolism of rat pancreatic islets in vitro. Endocrinology. 1990;126(2):1288-94.
73.Madeddu C, Mantovani G, Gramignano G, Astara G, Macciò A. Muscle wasting as main evidence of energy impairment in cancer cachexia: future therapeutic approaches. Future Oncology. 2015;11(19):2697-710.
74.Epstein RS, Basu Roy UK, Aapro M, Salimi T, Moran D, Krenitsky J, Leone-Perkins ML, Girman C, Schlusser C, Crawford JJPp, adherence. Cancer patients' perspectives and experiences of chemotherapy-induced myelosuppression and its impact on daily life2021:453-65.
75.Lazzari G, Silvano GJO, therapy. From anemia to erythropoietin resistance in head and neck squamous cell carcinoma treatment: a carousel driven by hypoxia2020:841-51.
76.Chung J, Bauer DE, Ghamari A, Nizzi CP, Deck KM, Kingsley PD, Yien YY, Huston NC, Chen C, Schultz IJ. The mTORC1/4E-BP pathway coordinates hemoglobin production with L-leucine availability. Science signaling. 2015;8(372):ra34-ra.

77.Doulatov S, Notta F, Laurenti E, Dick JE. Hematopoiesis: a human perspective. Cell stem cell. 2012;10(2):120-36.
78.Paulson RF, Hariharan S, Little JAJEh. Stress erythropoiesis: definitions and models for its study2020;89:43-54. e2.
79.Benedik PS, Hamlin SK. The physiologic role of erythrocytes in oxygen delivery and implications for blood storage. Critical Care Nursing Clinics. 2014;26(3):325-35.
80.Jewell UR, Kvietikova I, Scheid A, Bauer C, Wenger RH, Gassmann M. Induction of HIF–1α in response to hypoxia is instantaneous. The FASEB Journal. 2001;15(7):1312-4.
81.Semenza GL. Surviving ischemia: adaptive responses mediated by hypoxia-inducible factor 1. The Journal of clinical investigation. 2000;106(7):809-12.
82.Zheng H, Jiang L, Tsuduki T, Conrad M, Toyokuni SJRb. Embryonal erythropoiesis and aging exploit ferroptosis2021;48:102175.
83.Tsiftsoglou ASJC. Erythropoietin (EPO) as a key regulator of erythropoiesis, bone remodeling and endothelial transdifferentiation of multipotent mesenchymal stem cells (MSCs): implications in regenerative medicine2021;10(8):2140.
84.Bennett G, Kay M. Homeostatic removal of senescent murine erythrocytes by splenic macrophages. Experimental hematology. 1981;9(3):297-307.
85.Palis J. Primitive and definitive erythropoiesis in mammals. Frontiers in physiology. 2014;5:3.
86.Ludwig H, Van Belle S, Barrett-Lee P, Birgegård G, Bokemeyer C, Gascón P, Kosmidis P, Krzakowski M, Nortier J, Olmi P. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. European journal of cancer. 2004;40(15):2293-306.
87.Men JG, Tang J, Ding J, Chen X, Su J-M, Liu J-Y. Prevalence and characteristics of anemia in patients with solid cancers at diagnosis in southwest China. Asian Pacific Journal of Cancer Prevention. 2011;12:2825-8.
88.Hassan B, Yusoff Z, Hassali MA, Othman SB. Association and correlation of different chemotherapeutic regimens and doses with onset and severity of anemia among solid cancer patients. Asian Pac J Cancer Prev. 2011;12(10):2753-8.
89.Hassan BAR, Yusoff ZBM. Treatment patterns and outcomes in management of solid cancer patients suffering from anemia in Penang hospital. Asian Pac J Cancer Prev. 2011;12(6):1573-6.
90.Auerbach M, Muñoz M. Intravenous iron for treating cancer-induced anemia: meeting an unmet need? Chin Clin Oncol. 2012;1:21-3.
91.Auerbach M, Ballard H, Trout JR, McIlwain M, Ackerman A, Bahrain H, Balan S, Barker L, Rana J. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. Journal of Clinical Oncology. 2004;22(7):1301-7.
92.Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A, editors. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo clinic proceedings; 2015: Elsevier.
93.Baek JH, D'Agnillo F, Vallelian F, Pereira CP, Williams MC, Jia Y, Schaer DJ, Buehler PW. Hemoglobin-driven pathophysiology is an in vivo consequence of the red blood cell storage lesion that can be attenuated in guinea pigs by haptoglobin therapy. The Journal of clinical investigation. 2012;122(4):1444-58.
94.Grogan M, Thomas GM, Melamed I, Wong FL, Pearcey RG, Joseph PK, Portelance L, Crook J, Jones KD. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. Cancer. 1999;86(8):1528-36.
95.Newhall D, Oliver R, Lugthart SJNJM. Anaemia: A disease or symptom2020;78(3):104-10.
96.Dugan C, MacLean B, Cabolis K, Abeysiri S, Khong A, Sajic M, Richards T, Anaesthesia WsHrCJ. The misogyny of iron deficiency2021;76:56-62.
97.Bhadra P, Deb AJIJoNS. A review on nutritional anemia2020;10(59):18466-74.
98.Mattiello V, Schmugge M, Hengartner H, von der Weid N, Renella R, pediatrics SPHWGJEjo. Diagnosis and management of iron deficiency in children with or without anemia: consensus recommendations of the SPOG Pediatric Hematology Working Group2020;179:527-45.
99.Anand S, Burkenroad A, Glaspy JJCAHO. Workup of anemia in cancer2020;18(10):640-6.
100.Dainiak N, Kulkarni V, Howard D, Kalmanti M, Dewey MC, Hoffman R. Mechanisms of abnormal erythropoiesis in malignancy. Cancer. 1983;51(6):1101-6.
101.Doll DC, Weiss RB. Chemotherapeutic agents and the erythron. Cancer Treatment Reviews. 1983;10(3):185-200.
102.Miller CB, Jones RJ, Piantadosi S, Abeloff MD, Spivak JL. Decreased erythropoietin response in patients with the anemia of cancer. New England Journal of Medicine. 1990;322(24):1689-92.
103.Bokemeyer C, Oechsle K, Hartmann JT. Anaemia in cancer patients: pathophysiology, incidence and treatment. European journal of clinical investigation. 2005;35:26-31.
104.Mesa R, Gerds A, Vannucchi A, Al-Ali HK, Lavie D, Kuykendall A, Grosicki S, Iurlo A, Goh YT, Lazaroiu MJJoON, Survivorship. MOMENTUM: Phase 3 randomized study of momelotinib (MMB) versus danazol (DAN) in symptomatic and anemic myelofibrosis (MF) patients previously treated with a JAK inhibitor2022;13(11).
105.Mhaskar R, Wao H, Miladinovic B, Kumar A, Djulbegovic B. The role of iron in the management of chemotherapy-induced anemia in cancer patients receiving erythropoiesis-stimulating agents. Cochrane Database of Systematic Reviews. 2016(2).
106.Fishbane S, Kowalski EA, editors. The comparative safety of intravenous iron dextran, iron saccharate, and sodium ferric gluconate. Seminars in dialysis; 2000: Wiley Online Library.
107.Baribeault D, Auerbach M. Iron replacement therapy in cancer-related anemia. American Journal of Health-System Pharmacy. 2011;68(10_Supplement_1):S4-S14.
108.Rodgers III G, Gilreath J, Achebe M, Alwan L, Arcasoy M, Ali Beth S. NCCN. Cancer-and Chemotherapy-Induced Anemia, Version 2.2017. 2017.
109.Birgegård G, Henry D, Glaspy J, Chopra R, Thomsen LL, Auerbach M. A randomized noninferiority trial of intravenous iron isomaltoside versus oral iron sulfate in patients with nonmyeloid malignancies and anemia receiving chemotherapy: the PROFOUND trial. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2016;36(4):402-14.
110.Steensma DP, Sloan JA, Dakhil SR, Dalton R, Kahanic SP, Prager DJ, Stella PJ, Rowland Jr KM, Novotny PJ, Loprinzi CL. Phase III, randomized study of the effects of parenteral iron, oral iron, or no iron supplementation on the erythropoietic response to darbepoetin alfa for patients with chemotherapy-associated anemia. Journal of Clinical Oncology. 2011;29(1):97.
111.Gabrilove JL, Cleeland CS, Livingston RB, Sarokhan B,

Winer E, Einhorn LH. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. Journal of Clinical Oncology. 2001;19(11):2875-82.
112.Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. Blood, The Journal of the American Society of Hematology. 2010;116(23):4754-61.
113.Ludwig H, Aapro M, Bokemeyer C, Glaspy J, Hedenus M, Littlewood TJ, Österborg A, Rzychon B, Mitchell D, Beguin Y. A European patient record study on diagnosis and treatment of chemotherapy-induced anaemia. Supportive Care in Cancer. 2014;22:2197-206.
114.Naoum FA. Iron deficiency in cancer patients. Revista brasileira de hematologia e hemoterapia. 2016;38:325-30.
115.Aapro M, Beguin Y, Bokemeyer C, Dicato M, Gascón P, Glaspy J, Hofmann A, Link H, Littlewood T, Ludwig H. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. Annals of Oncology. 2018;29:iv96-iv110.
116.Mustafai FA, Balouch A, Abdullah, Jalbani N, Bhanger MI, Jagirani MS, Kumar A, Tunio A. Microwave-assisted synthesis of imprinted polymer for selective removal of arsenic from drinking water by applying Taguchi statistical method. European Polymer Journal. 2018;109:133-42. doi: https://doi.org/10.1016/j.eurpolymj.2018.09.041.
117.Weigl A, Köhler N, Monsef I, Bohlius J, Kuhr K, Becker I, Skoetz N. Intravenous iron versus oral iron versus no iron with or without erythropoiesis-stimulating agents (ESA) for cancer patients with anaemia: A systematic review and network meta-analysis. The Cochrane Database of Systematic Reviews. 2017;2017(4).
118.Birgegård G, Aapro MS, Bokemeyer C, Dicato M, Drings P, Hornedo J, Krzakowski M, Ludwig H, Pecorelli S, Schmoll H-J. Cancer-related anemia: pathogenesis, prevalence and treatment. Oncology. 2005;68(Suppl. 1):3-11.
119.Henry D, Brooks Jr B, Case Jr D, Fishkin E, Jacobson R, Keller A, Kugler J, Moore J, Silver R, Storniolo A. Recombinant human erythropoietin therapy for anemic cancer patients receiving cisplatin chemotherapy. The cancer journal from Scientific American. 1995;1(4):252-60.
120.Vansteenkiste J, Glaspy J, Henry D, Ludwig H, Pirker R, Tomita D, Collins H, Crawford J. Benefits and risks of using erythropoiesis-stimulating agents (ESAs) in lung cancer patients: study-level and patient-level meta-analyses. Lung Cancer. 2012;76(3):478-85.
121.Thorp ML, Johnson ES, Yang X, Petrik AF, Platt R, Smith DH. Effect of anaemia on mortality, cardiovascular hospitalizations and end-stage renal disease among patients with chronic kidney disease. Nephrology. 2009;14(2):240-6.
122.Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, Trelle S, Weingart O, Bayliss S, Djulbegovic B. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. Journal of the National Cancer Institute. 2006;98(10):708-14.
123.NELSON AH, FLEISHER LA, ROSENBAUM SH. Relationship between postoperative anemia and cardiac morbidity in high-risk vascular patients in the intensive care unit. Critical care medicine. 1993;21(6):860-6.
124.Watkins T, Surowiecka MK, McCullough J. Transfusion indications for patients with cancer. Cancer Control. 2015;22(1):38-46.
125.Eder AF, Chambers LA. Noninfectious complications of blood transfusion. Archives of pathology & laboratory medicine. 2007;131(5):708-18.
126.Koeller JM. Clinical guidelines for the treatment of cancer-related anemia. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 1998;18(1):156-69.
127.Schrijvers D. Management of anemia in cancer patients: transfusions. The oncologist. 2011;16(S3):12-8.
128.Bryer E, Henry D. Chemotherapy-induced anemia: etiology, pathophysiology, and implications for contemporary practice. International Journal of Clinical Transfusion Medicine. 2018:21-31.
129.Spivak JL, Gascón P, Ludwig H. Anemia management in oncology and hematology. The oncologist. 2009;14(S1):43-56.
130.Javarappa KK, Tsallos D, Heckman CA. A multiplexed screening assay to evaluate chemotherapy-induced myelosuppression using healthy peripheral blood and bone marrow. SLAS DISCOVERY: Advancing Life Sciences R&D. 2018;23(7):687-96.
131.Taylor SJ, Duyvestyn JM, Dagger SA, Dishington EJ, Rinaldi CA, Dovey OM, Vassiliou GS, Grove CS, Langdon WY. Preventing chemotherapy-induced myelosuppression by repurposing the FLT3 inhibitor quizartinib. Science translational medicine. 2017;9(402):eaam8060.
132.Masoud GN, Li W. HIF-1α pathway: role, regulation and intervention for cancer therapy. Acta Pharmaceutica Sinica B. 2015;5(5):378-89.
133.Miller RL, Sandoval PC, Pisitkun T, Knepper MA, Hoffert JD. Vasopressin inhibits apoptosis in renal collecting duct cells. American journal of physiology-renal physiology. 2013;304(2):F177-F88.
134.Carrancio S, Markovics J, Wong P, Leisten J, Castiglioni P, Groza MC, Raymon HK, Heise C, Daniel T, Chopra R. An activin receptor II A ligand trap promotes erythropoiesis resulting in a rapid induction of red blood cells and haemoglobin. British Journal of Haematology. 2014;165(6):870-82.
135.Madeddu C, Gramignano G, Astara G, Demontis R, Sanna E, Atzeni V, Macciò A. Pathogenesis and treatment options of cancer related anemia: perspective for a targeted mechanism-based approach. Frontiers in physiology. 2018;9:1294.
136.Gilreath JA, Rodgers GM. How I treat cancer-associated anemia. Blood, The Journal of the American Society of Hematology. 2020;136(7):801-13.
137.Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine—blood transfusion. New England journal of medicine. 1999;340(6):438-47.