

Anemia Management in Oncology and Hematology

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ABSTRACT

Anemia is frequent in cancer patients and its incidence increases with chemotherapy. The probability of requiring transfusions also increases with chemotherapy. Anemia negatively impacts survival and accentuates fatigue in cancer patients. Cancer promotes inflammatory cytokine production, which suppresses erythropoiesis and erythropoietin (EPO) production. Erythropoiesis-stimulating agents (ESAs) improve erythropoiesis and reduce transfusion needs in anemic cancer patients receiving chemotherapy. However, meta-analyses have shown an increased risk of thromboembolic (TE) events with ESA use during chemotherapy, but not increased on-study mortality or reduced overall survival. Three reasons have been proposed to explain why ESAs might have adverse effects in anemic cancer patients: tumor progression due to stimulation of tumor cell EPO receptors; increased risk of TE; and reduced survival. However, erythropoietin is not an on-

cogene, nor is the EPO receptor. It has also been demonstrated that erythropoietin does not stimulate tumor proliferation. Increased TE risk associated with ESAs is probably a consequence of increased blood viscosity due to excessive RBC mass elevation with concomitant plasma volume contraction, nitric oxide scavenging, and endothelial cell activation. Increased ESA dosing may also impact survival negatively because EPO contracts the plasma volume and stimulates inflammatory cytokine production independently of increasing erythropoiesis. Furthermore, transfusions themselves are associated with an increase in TE and plasma volume contraction, and these events are potentiated when ESAs are given with transfusions. An update on the management of anemia in oncology, the potential adverse events of ESAs, the benefits and risks of transfusions, and QoL are discussed in this paper. *The Oncologist* 2009;14(suppl 1):43–56

INTRODUCTION

Anemia is common and can be profound in cancer patients. The prevalence of anemia in solid tumor patients is close to 40% [1, 2], and the frequency of anemia increases with the duration of chemotherapy. In hematological malignancies,

the prevalence of anemia is almost double that found in solid tumors [3].

Chemotherapy is one of the most important causes of anemia in cancer patients and the association between dose and duration of chemotherapy with anemia is well known

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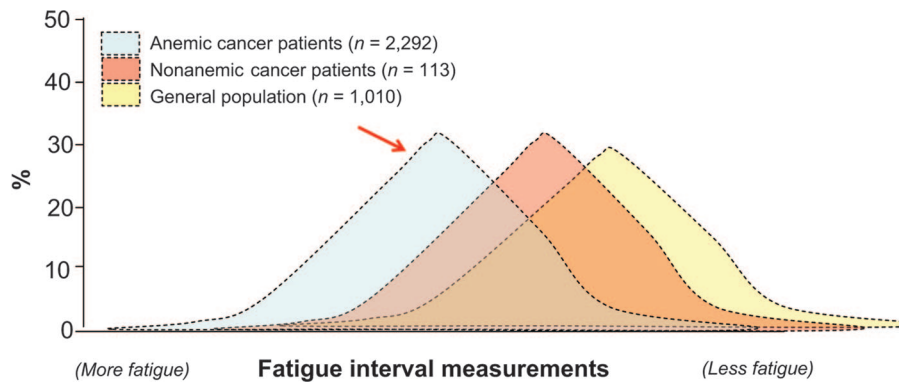


Figure 1. Fatigue is worse in anemic cancer patients [12].

[4]. However, the negative impact that anemia has on the cancer patient in terms of survival and quality of life (QoL) also deserves attention.

Anemia is associated with shorter survival in cancer patients and this association has been established for almost all types of cancer studied [5]. For instance, anemic lymphoma patients have significantly lower overall survival and progression-free survival rates than nonanemic patients [6]. Similarly, the overall survival time for anemic patients receiving radiotherapy for head and neck (H&N) cancer was less than that of nonanemic patients [7]. Patient age also has a negative impact in this regard; older patients who are anemic have a shorter survival duration than their nonanemic counterparts [8].

Anemia also impacts tumor behavior. The transcription factor hypoxia-inducible factor (HIF)-1 α plays an important role in response to hypoxia [9]. H&N cancer patients who have a substantial increase in tumor HIF-1 α have a shorter survival time than patients with tumors that are not hypoxic ($p = .008$) [9]. This is also true for patients with cervical cancer, for whom a higher mortality rate is seen in patients with hypoxic tumors than in those with nonhypoxic tumors ($p = .0039$) [10]. Hypoxia not only induces changes in the expression of genes that promote angiogenesis, but it also promotes a more aggressive phenotype by selecting for *p53* mutations. Such mutations allow cells to escape cell cycle arrest and become genetically more unstable, leading to greater tumor aggressiveness and a poorer prognosis [10].

CONSEQUENCES OF ANEMIA

The consequences of anemia on the whole body are profound. Impaired tissue oxygenation leads to the generation of angiogenic factors that may promote tumor growth. There is also: impaired organ function, reduced QoL, greater postoperative mortality, greater iron absorption if erythropoiesis is ineffective, a higher probability of blood transfusion after chemotherapy, lower sensitivity to chemo-

therapy, and shorter survival. With ineffective erythropoiesis, iron absorption steadily increases [11]. This is an important consideration, particularly because the administration of i.v. iron is now in vogue in anemic cancer patients receiving erythropoiesis-stimulating agents (ESAs). Of course, cancer itself increases inflammatory cytokine production, which can activate hepcidin synthesis and increase intracellular iron, whereas transfusions themselves increase the body's iron burden. Furthermore, increased intracellular iron enhances HIF-1 α degradation, resulting in reduced erythropoietin (EPO) production.

Anemia accentuates fatigue in cancer patients [12]. Although fatigue is not specific to cancer patients, it appears to be greater in these patients, and fatigue in anemic cancer patients is decidedly worse (Fig. 1) [12].

From various studies over the years, it is now possible to predict which cancer patients receiving chemotherapy are most likely to develop anemia [13]. Significant predictive factors for the risk of developing anemia include: a low initial hemoglobin (Hb) level (≤ 12.9 g/dl in females and ≤ 13.4 g/dl in males), having lung or gynecologic cancers versus gastrointestinal (GI) or colorectal cancers, cancer at any site other than the GI tract or colon/rectum, treatment with platinum chemotherapy, and female gender [13]. In lymphoma and multiple myeloma patients, factors found to significantly increase anemia risk were a low initial Hb level, persistent or resistant disease, platinum chemotherapy, and female gender [3]. Thus, it is feasible to define which patients might benefit from ESAs.

CAUSES OF CANCER-ASSOCIATED ANEMIA

In cancer, as in renal disease, there are many causes for anemia other than a lack of EPO, as shown in Figure 2 [14]. This discussion focuses on cytokine production because cancer induces inflammatory cytokine production and inflammatory cytokines suppress erythroid progenitor cell proliferation as well as EPO production. For example, in

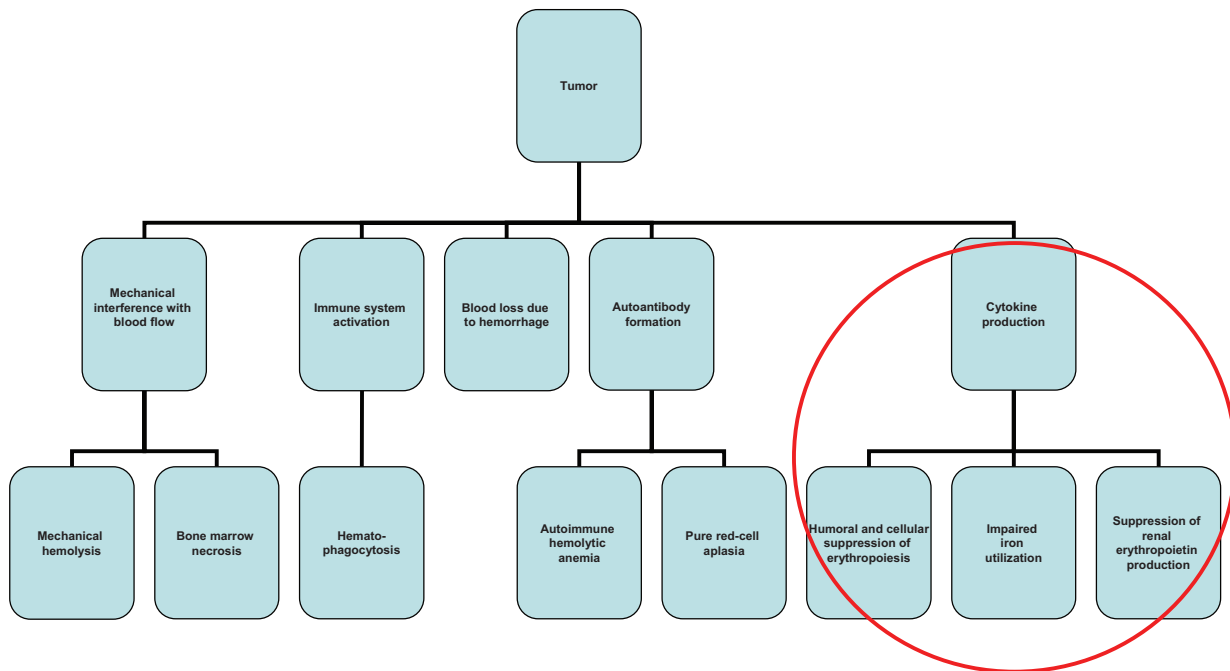


Figure 2. Causes of cancer-associated anemia [14].

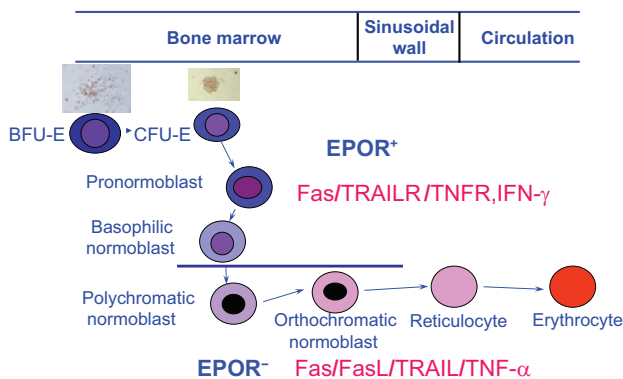


Figure 3. Erythropoiesis.

Abbreviations: CFU-E, colony-forming units–erythroid; EPOR, erythropoietin receptor; IFN, interferon; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor receptor apoptosis-inducing ligand.

ovarian cancer patients, serum levels of inflammatory cytokines—interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF)- α —correlated inversely with Hb levels [15]. Hb levels were lower and inflammatory cytokine levels were higher in advanced stage ovarian cancer [15].

Figure 3 shows the progression of erythroid progenitor cells from their initial commitment to the formation of mature RBCs. Importantly, RBC progenitors express receptors for inflammatory cytokines, which are necessary for normal differentiation, but in the absence of EPO, these cytokines actually promote erythroid cell death.

Table 1 shows the four essential factors involved in erythropoiesis. Impairment of any of these will inhibit

Table 1. Essential factors in erythropoiesis and the effect of inflammation, infection, or cancer

Factor	Effect
Intensity of the stimulus	Erythropoietin production is suppressed by cytokines and iron overload
Functional capacity of the bone marrow	Erythroid progenitor cell proliferation is suppressed by cytokines and erythropoietin lack
Available nutrients	Iron is sequestered and protein synthesis is reduced (hepcidin and cytokines)
RBC survival	RBC count is reduced and blood loss is increased because of diagnostic testing

erythropoiesis. In cancer patients, EPO production is suppressed by inflammatory cytokines. Importantly, EPO production is also suppressed by iron overload, because the prolyl hydroxylases, which target HIF-1 α (the transcription factor responsible for *EPO* gene transcription) for ubiquitination, are sensitive to intracellular iron concentration as well as oxygen tension. If the intracellular iron concentration is low, prolyl hydroxylation is inhibited; if iron concentration is increased, prolyl hydroxylation of HIF-1 α is enhanced. Inflammatory cytokines also suppress erythroid progenitor cell proliferation directly. RBC survival is also reduced in inflammatory states and, of course, blood

loss is increased as a result of diagnostic testing. Impaired iron use in the anemia of cancer is characterized by increased reticuloendothelial iron stores, low serum iron, reduced iron absorption, decreased serum transferrin, decreased transferrin saturation, increased serum ferritin, and increased erythrocyte-free protoporphyrin [16]. It is likely that decreased EPO production and inhibition of its activity by inflammatory cytokines are responsible for abnormalities such as reduced iron absorption and decreased erythroblast transferrin-receptor expression [16]. The role of iron metabolism in anemia is discussed in further detail in this supplement in the article by Anatole Besarab, Walter Hörl, and Donald Silverberg [17].

RECOMBINANT HUMAN EPO

The ESAs permit anemia correction and reduce RBC transfusion needs. ESAs rank among the most successful products of recombinant DNA technology. For example, during initial phase III clinical trials, recombinant human EPO alleviated anemia and abrogated transfusions in 97% of anemic patients with end-stage renal disease (ESRD).

Thus, there was adequate rationale for the use of recombinant EPO in the management of anemia in cancer patients. Anemia is an adverse prognostic factor in cancer patients and anemia is a risk factor for transfusion following chemotherapy. Anemia is also a component of cancer-related fatigue. Anemia developing during treatment is a risk factor for locoregional radiation therapy failure and shorter post-therapy survival. Anemia also correlates with tumor hypoxia, a measure of radiation resistance. As mentioned above, EPO production is suppressed in cancer patients and erythropoiesis is suppressed in cancer patients independently of EPO lack because of a cytokine storm that also impairs proper use of iron by erythropoietic precursors. EPO therapy can alleviate the need for transfusions. Finally, EPO therapy improved QoL in anemic ESRD patients.

In both patients with hematologic malignancies and those with solid tumors, there was a clear increase in Hb levels in patients receiving the ESA epoetin alfa, versus placebo ($p < .001$) [18, 19]. Initially, oncologists and hematologists followed nephrologists in giving epoetin alfa at a dose of 150 IU/kg s.c. three times per week, [18], but they subsequently found that s.c. dosing of epoetin alfa at 30,000–40,000 IU once per week was equally effective [20]. Once weekly dosing also provided a convenience factor for patients. For further patient convenience, ESAs with less frequent dosing regimens (i.e., administered once every 2 weeks or once every 3 weeks) were also developed [21, 22]. However, higher ESA doses (60,000–80,000 IU)

are needed with this expanded time interval to maintain target Hb levels.

In an early clinical trial, epoetin alfa appeared to produce longer survival in anemic cancer patients with either a solid tumor or a hematological malignancy, compared with placebo, although the trial was not powered to substantiate this finding [18]. Therefore, the possibility that EPO might improve survival among anemic cancer patients became a new clinical trial objective.

Meta-analysis of clinical trials employing recombinant EPOs also showed that patients receiving EPO had fewer transfusions, almost in a 2:1 ratio, than patients not receiving ESAs (odds ratio, 0.41; 95% confidence interval [CI], 0.33–0.5; $p < .00001$) [23]. An early Cochrane meta-analysis also confirmed that cancer patients receiving ESAs had a lower risk for having a blood transfusion than untreated patients (relative risk, 0.67; 95% CI, 0.62–0.73) [19]. In this first Cochrane meta-analysis, patients receiving ESAs also had an apparent survival advantage over untreated patients (adjusted data: hazard ratio [HR], 0.81; 95% CI, 0.67–0.99; unadjusted data: HR, 0.84; 95% CI, 0.69–1.02) [19].

Potential Adverse Effects of the Recombinant Human EPOs in Oncology Patients

Based on the possibility that recombinant EPOs might provide a survival advantage for anemic cancer patients, a large number of clinical trials have been conducted. Most, however, differed from the early clinical trials primarily by attempting to normalize hematocrit or starting the ESA at a normal hematocrit. These approaches proved to be disadvantageous, and in 2007, the U.S. Food and Drug Administration (FDA) issued a black box warning for the recombinant EPOs, warning of greater mortality, serious cardiovascular and thromboembolic (TE) events, and tumor progression.

Four of these clinical trials can serve as paradigms for the events that initiated FDA action. A higher mortality rate was observed in patients receiving recombinant EPO than in control patients in H&N cancer (Erythropoietin to treat anemia in head and neck cancer patients, ENHANCE study) and breast cancer (Breast cancer erythropoietin survival trial, BEST study) patients receiving radiation or chemotherapy, and in anemic cancer patients not receiving chemotherapy (EPO-CAN-20 non-small cell lung cancer [NSCLC] study and Amgen 103 study). These particular studies are discussed in further detail elsewhere in this issue, but a Cochrane meta-analysis of all such studies found that patients who did not receive an ESA had a longer survival time than those who did [8]. Importantly, the meta-analysis also showed that there was a higher risk for TE events in patients receiving an ESA than in controls [24]. These results should not be surprising when one considers

that in 1993 the FDA approved the use of recombinant EPO in anemic cancer patients receiving chemotherapy based on data from only 413 patients in three studies (Table 2). By 2007, data were available on 11,757 patients in 59 studies.

In December 2008, an individual patient data meta-analysis of the effects of ESAs on mortality in cancer patients was presented at the American Society of Hematology meeting, which was published in 2009 [25]. In 13,933 cancer patients receiving ESAs, including those not receiving chemotherapy, there was a significantly greater relative risk for on-study mortality (HR, 1.17; $p = .002$) and a significantly greater relative risk for a shorter overall survival duration (HR, 1.06; $p = .005$) [25]. Of these 13,933 cancer patients, 10,441 patients received chemotherapy. Within this latter group of patients, there was a higher relative risk for on-study mortality (HR, 1.10) and for shorter overall survival (HR, 1.04) in the patients who received ESAs; however, these differences were not statistically significant ($p = .12$ and $p = .26$, respectively) [25].

The meta-analyses are discussed in further detail in the manuscript by Matti Aapro and Jerry Spivak in this supplement [26].

There are three major reasons to explain why the recombinant EPOs could have potential adverse effects in anemic cancer patients: tumor progression resulting from stimulation of tumor cell EPO receptors, a higher risk for TE events, and a shorter survival duration because of recombinant EPO itself.

Tumor Progression Resulting from Stimulation of Tumor Cell EPO Receptors

Are the recombinant EPOs tumor promoters?

EPO is not an oncogene. Constitutive production of EPO is not associated with a higher incidence of cancer. The gene encoding the EPO receptor is not an oncogene. Constitutive EPO receptor activation induces erythrocytosis but not hematopoietic malignancies [27]. In addition, currently available EPO receptor antibodies lack specificity and generally identify heat shock protein (hsp)70, a poor prognosis tumor marker [28]. Although a recent study suggested that preabsorption of the currently used EPO receptor antiserum C20 with an hsp70 peptide improved antibody specificity for plasma membrane-associated protein, the study was done using NSCLC tissue microarrays, only 30% of the tumors retained membrane staining, and no control tissue was studied to confirm antibody specificity for the EPO receptor in this system [29]. Reports using such antibodies to demonstrate EPO receptor expression in tumor cells by immunohistochemistry or immunoblotting should, therefore, be viewed with caution.

In this regard, studies suggesting that EPO stimulates

Table 2. Analyses of recombinant erythropoietin therapy in cancer patients

Type of analysis	n of patients
U.S. FDA approval (1993)	413 (3 studies)
ASH/ASCO meta-analysis (2002)	1,927 (22 studies)
Cochrane meta-analysis (2005)	3,287 (27 studies)
Cochrane meta-analysis (2006)	9,353 (57 studies)
ASH/ASCO meta-analysis (2007)	11,757 (59 studies)
Cochrane IPD meta-analysis (2008)	13,933 (53 studies)

Abbreviations: ASH/ASCO, American Society of Hematology/American Society of Clinical Oncology; FDA, Food and Drug Administration; IPD, individual patient data.

tumor cell proliferation or enhances tumor cell function have used immortalized cell lines rather than primary tissue [30, 31], forced overexpression of the EPO receptor [32], or nonphysiologic concentrations of EPO [33, 34]. When pharmacologic concentrations of EPO were employed using NSCLC cell lines, activation of the Janus kinase 2/signal transducer and activator of transcription 5, Ras/extracellular signal-related kinase, and phosphatidylinositol 3' kinase/Akt pathways was observed, but this did not impart a growth advantage to these cells [30]. Furthermore, a number of other studies have shown that EPO does not stimulate tumor growth in vitro or in vivo. Recombinant EPO did not stimulate tumor growth in xenografted mouse tumors [35] and potentiated the positive effects of radiation therapy [36]. Retrospective studies also showed that recombinant EPO prolonged survival in myelodysplastic syndrome (MDS) patients and did not accelerate leukemic transformation [37].

From a physiological perspective, there are more EPO receptors on erythroid cells than on nonerythroid cells or tumor cells, and EPO receptor–ligand affinity on cells other than erythroid cells is so low that the competition for EPO is almost nonexistent at plasma EPO concentrations realized during chemotherapy. These facts, in addition to the above cited arguments, undermine the postulate that recombinant EPO promotes tumor growth.

Joachim Fandrey and Mario Dicato discuss ESAs and tumor proliferation in further detail in their manuscript in this supplement [38].

INCREASED RISK FOR TE EVENTS

The increased risk for TE events in anemic cancer patients can be explained by the effects of EPO on the RBC mass and the plasma volume in the setting of the hypercoagulability that is characteristic of cancer.

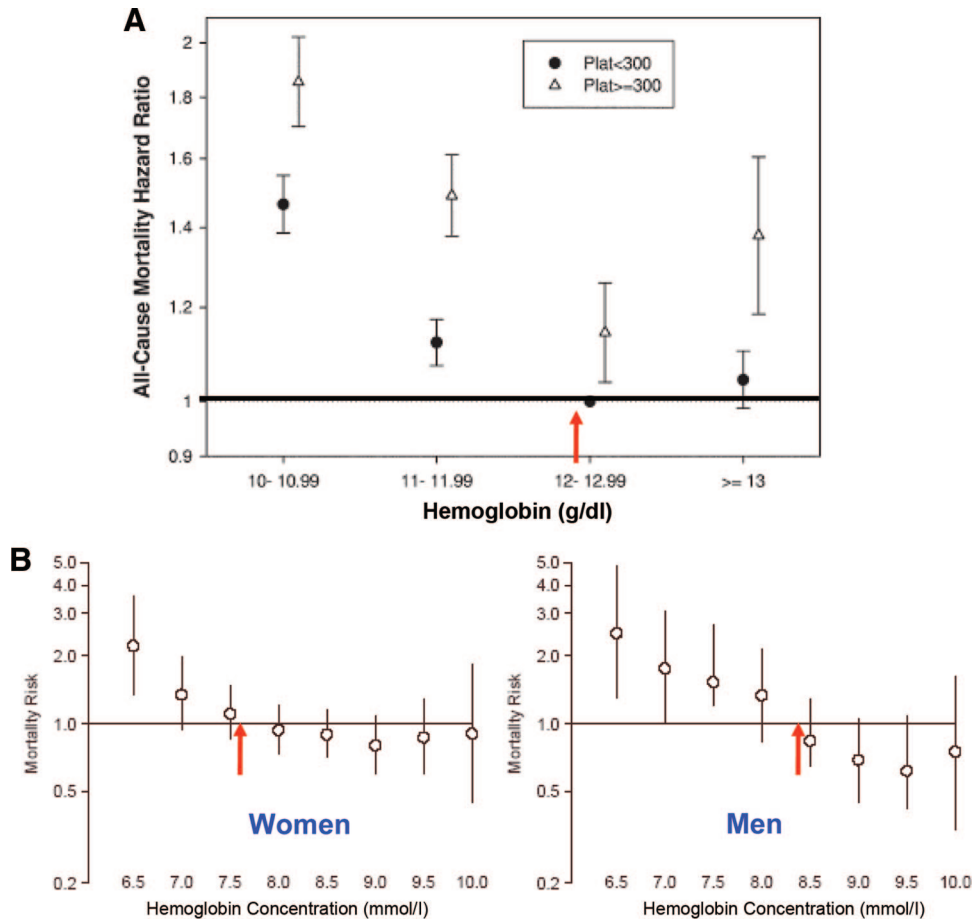


Figure 4. The hemoglobin–mortality threshold. **(A):** All-cause mortality hazard ratio by hemoglobin level (g/dl). Reprinted from Streja E, Kovesdy CP, Greenland S et al. Erythropoietin, iron depletion, and relative thrombocytosis: A possible explanation for hemoglobin-survival paradox in hemodialysis. *Am J Kidney Dis* 2008;52:727–736, with permission from Elsevier. **(B):** Mortality risk by hemoglobin concentration (mmol/l) in women and men (1 mmol/l = 1.6 g/dl, 7.5 mmol/l = 12 g/dl). Reprinted with permission from Izaks GJ, Westendorp RG, Knook DL. The definition of anemia in older persons. *JAMA* 1999;281:1714–1717. Copyright © 1999 American Medical Association. All rights reserved.

RBC Mass Effects

An expanded RBC mass can cause systemic hypertension; pulmonary hypertension; decreased renal blood and cerebral blood flow; generation of platelet microparticles; enhanced platelet, leukocyte, and endothelial cell interactions; aspirin resistance resulting from erythrocyte adenosine uptake; a higher risk for thrombosis because of hyperviscosity; vasoconstriction resulting from nitrous oxide scavenging; greater infarct size; and a hemorrhagic diathesis at very high hematocrits.

Even within the normal range of hematocrit, mortality risk is associated with both increasing and decreasing Hb concentrations (12 to ≥ 13 g/dl). The Hb–mortality threshold is around 12 g/dl in either direction (Fig. 4) regardless of the underlying cause of anemia [39, 40].

Plasma volume expansion may also mask the true hematocrit in cancer patients. Some cancer patients who appear to be anemic according to their hematocrit actually

have an increased plasma volume, and are not anemic by direct blood volume measurements [41]. Thus, some apparently anemic cancer patients who are receiving ESAs may actually have a normal RBC mass. In addition, in other patients, the hematocrit is being raised higher than it should be based on the data in Figure 4.

There is an optimal Hb level for oxygen transport that varies according to the size of the blood volume [42]. As the Hb level goes up, oxygen transport goes up until a Hb level is achieved beyond which oxygen transport falls because of hyperviscosity [42]. Interestingly, changes in QoL follow a similar curve with respect to Hb level. As the Hb level increases to a normal level, QoL increases [42]. However, when the Hb level increases further, QoL decreases [42].

Plasma Volume Effects

There is a correlation between hematocrit and cardiac output in ESRD patients [43]. When an anemic renal disease

patient is transfused, peripheral vascular resistance increases, systolic blood pressure increases, and the cardiac index decreases as the hematocrit increases [43]. These changes are associated with a decrease in plasma volume because of the body's tendency to maintain a constant blood volume. In the same way, an increase in RBC mass induced by EPO is associated with a reduction in plasma volume.

It should not be surprising, therefore, that recombinant EPO and blood transfusions when given together appear to be additive with respect to developing venous thrombosis. In a study of anemic cervical cancer patients receiving concurrent radiation and cisplatin, whose Hb level was maintained >12 g/dl with the use of recombinant EPO, the incidence of TE events was highest in those patients who had received both an ESA *and* transfusions, compared with those who had received either treatment alone [44]. This suggests that caution should be exercised when both ESAs and transfusions are given together. This is discussed in greater detail elsewhere in this issue.

Platelet Effects

In a prospective, multicenter observational study of venous thromboembolism in cancer patients receiving chemotherapy, platelet counts $\geq 350,000/\text{mm}^3$ were associated with a higher incidence of thrombosis (odds ratio, 2.81; 95% CI, 1.63–4.93; $p = .0002$) independent of recombinant EPO therapy [45]. It was therefore suggested that a high prechemotherapy platelet count could be a marker that could help identify patients at risk for venous thrombosis [45].

However, this correlation may have nothing to do with the platelet count per se. Rather, the platelet count may only be a surrogate marker of the inflammation associated with the increase in inflammatory cytokine synthesis that occurs with cancer. Recombinant EPO itself may also promote inflammatory cytokine production and contribute to this effect. In patients with chronic kidney disease not receiving dialysis, anemic patients receiving an ESA had a significantly higher TNF-1 α level and significantly lower serum albumin level, with trends toward higher IL-6 and IL-8 levels than in nonanemic patients [46]. The elevated platelet count in these patients was probably not a consequence of iron deficiency, but rather a reflection of an underlying inflammatory state.

This contention is supported by a study in which recombinant EPO was given i.v. to transfusion-dependent anemic ESRD patients and the effect of EPO therapy on marrow progenitor cell proliferation was evaluated [47]. In the post-treatment marrow, there was not only an increase in BFU-E and colony-forming units–erythroid (CFU-E) numbers, but also an increase in CFU-megakaryocytic (Mk) and CFU-granulocyte-macrophage (GM) numbers as well (Table 3)

Table 3. Effect of systemic erythropoietin therapy on marrow progenitor cell proliferation [47]

Progenitor cell	Fold increase	
	<i>n</i>	DNA synthesis
BFU-E	1.95	4.22
CFU-E	3.42	2.22
CFU-Mk	1.98	2.73
CFU-GM	1.73	1.88

Abbreviations: CFU, colony-forming units; E, erythroid; GM, granulocyte-macrophage; Mk, megakaryocytic.

[47]. The increased number of colony-forming cells was accompanied by a doubling of the percentage of cells in DNA synthesis [47]. Because EPO is not known to act on myeloid (CFU-GM) and megakaryocytic (CFU-Mk) progenitor cells, this could have occurred only if the recombinant EPO had stimulated the production or release of other cytokines.

Shorter Survival: The EPO Effect

Failure to respond to recombinant EPO appears, independently, to be a poor prognostic sign. In a meta-analysis of anemic renal disease patients receiving recombinant EPO, increasing the EPO dose was associated with a greater mortality rate independent of the Hb level achieved [39]. In a study of anemic cancer patients, those patients who failed to respond to recombinant EPO had a shorter survival duration than those patients who responded to the hormone [48].

Why should EPO nonresponsiveness or possibly its dose be a marker for mortality? Normally, with exposure to hypoxia, plasma EPO increases rapidly [49]. However, the high EPO level is rapidly downregulated to normal even though the hypoxia persists (Fig. 5A) [49]. Recombinant EPO was formerly given three times a week, but now the total dose is usually given once a week. When recombinant EPO is administered once a week, there is essentially recapitulation of the hypoxic situation, whereby EPO levels rapidly peak and are then downregulated [50]. Because the plasma volume contraction associated with hypoxia is probably a result, in part, of the increase in plasma EPO, once-weekly dosing, in which the plasma EPO level exceeds the concentration bound by erythroid cell EPO receptors, probably triggers both cytokine production and plasma volume contraction. In contrast, the lower plasma EPO level achieved with three times weekly administered recombinant EPO does not exceed erythroid cell receptor-binding capacity and may not trigger cytokine production or as much plasma volume contraction (Fig. 5B). Therefore, although it may sound retrogressive, it is possible that

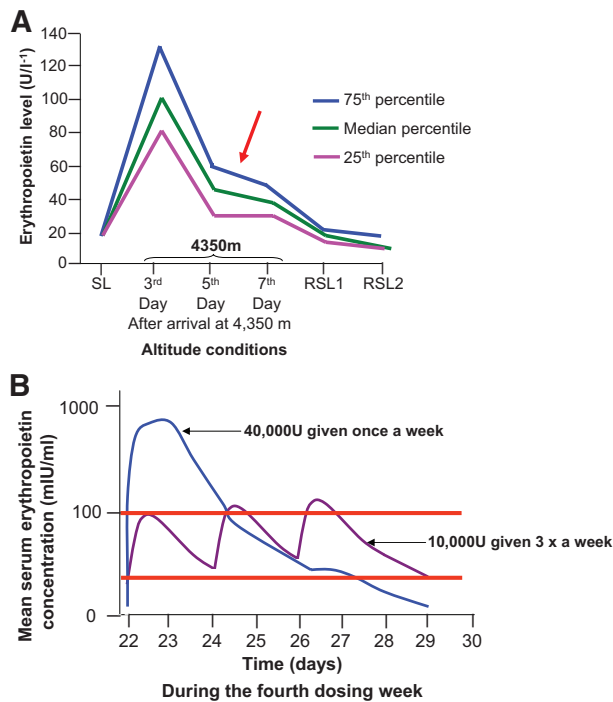


Figure 5. Comparison of the pharmacokinetics of endogenously produced and exogenously administered erythropoietin. **(A):** Downregulation of hypoxia-induced erythropoietin production during hypoxia [49]. Measurements were taken at sea level (SL), after the 3rd, 5th, and 7th days at an altitude of 4,350 m and 12 hours after returning to SL (RSL1) and 24 hours after returning to SL (RSL2). **(B):** Accumulation versus nonaccumulation kinetics with s.c. erythropoietin [50]. Mean serum erythropoietin concentration–time profiles for epoetin alfa, once weekly and three times a week dosing regimens, during the fourth dosing week.

a once-weekly recombinant EPO schedule might not be as safe as a three times per week schedule at a lower dose, a contention supported by the recent meta-analysis of 13,933 anemic cancer patients receiving an ESA [25].

BENEFITS/RISKS OF RBC TRANSFUSIONS

Some key dates in the history of blood transfusions include the introduction of the Australia antigen in 1963, which was the antigen for hepatitis B virus (HBV) and was used as a major screening tool for the blood supply, and the HIV epidemic (AIDS) in 1983, which led to the development of HIV tests used in blood banks from 1985 onward.

A blood transfusion consists of administering a blood component from a healthy individual to a patient to correct a blood component deficit. However, it is also very important to remember that a blood transfusion is also a tissue transplant whereby hematopoietic tissue from a healthy individual (donor) is transferred into a patient (recipient).

The two main adverse effects of blood transfusions are immunosuppression and transfusion reactions.

Immunosuppressive Effects

Measurements of immunologic function in patients who had received multiple transfusions showed that natural killer cell function was severely depressed in these patients [51]. Furthermore, with regard to transfusion-induced immunosuppression, allogeneic RBC transfusion was associated with a higher risk for cancer recurrence and postsurgical infection [52]. Retrospective and prospective studies found an association between the number of transfusions and colorectal cancer recurrence. Similar data were found for postsurgical infections. In the 1980s, blood transfusions were also given prior to renal transplants to take advantage of their immunosuppressive effect, although this is no longer the standard of care.

Most of the immunological problems with blood transfusions appear to be a consequence of leukocytes. When leukocytes are removed from stored blood, these problems are markedly reduced. However, it is difficult to completely remove all leukocytes from stored blood because they adhere to plastic bags. Leukocytes can release cytokines during platelet storage, resulting in nonhemolytic febrile reactions. Leukocyte contamination is the first cause of alloimmunization to human leukocyte antigens and to leukocyte-specific antigens. Leukocytes are the vectors responsible for the introduction of most viruses—Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus (HHV)-8—and toxoplasma into the recipient's system.

Transfusion Reactions

Some of the current known blood contaminants include hepatitis A virus, CMV, EBV, HHV-8, toxoplasma, parvovirus B-19, West Nile virus, spongiform encephalopathy prions, Chagas, *Babesia*, and malaria. With globalization and worldwide travel, there is a greater probability of people being infected and bringing infections to our blood banks, as was the case with the outbreak of West Nile virus in New York.

From 1969 to 1998, there has been a decreasing incidence (from 33% in 1969 to 0.3% in 1994) of transfusion-associated hepatitis in blood recipients [53]. As a result of better blood screening, it is now extremely rare to get an HBV infection from a blood transfusion [53].

Importantly, there is a time window of uncertainty of around 10–28 days during which the current systems can't detect certain viruses (Table 4). Therefore, there is still a risk for infection during this time period.

Transfusion reactions include febrile nonhemolytic transfusion reaction, bacterial infection, acute hemolytic reaction, anaphylactic reaction, transfusion-associated acute lung injury (TRALI), volume overload, iron overload, de-

Table 4. Transfusion time window of selected viruses

Virus	Time taken to detect virus in stored blood
HIV	10 days ^a
HIV p24	16 days
HTLV	28 days
HBV	20 days ^a
HCV	12 days ^a

^aThese values are obtained by screening blood samples using genomic analysis (polymerase chain reaction). In conventional assays, the time windows were: HIV, 22 days; HBV, 21 days; HCV, 21 days. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV, human T lymphotropic virus.

layed hemolytic reaction, transfusion-associated graft-versus-host disease, and post-transfusional purpura (Table 5) [54–62].

Safety

Delayed hemolytic reactions are the most frequent complications of blood transfusions, followed by TRALI, parvovirus B-19, bacterial contamination of platelets, and HBV and HCV infections.

The potential for viral and other pathogen infections is a concern for blood transfusion-related adverse events.

Currently, infectious causes of allogeneic blood transfusion (ABT)-related deaths account for <15% of all trans-

Table 5. Transfusion reactions [54–62]

Reaction	Description
Febrile nonhemolytic transfusion reaction	This is the most common reaction. Symptoms include fever and dyspnea, 1–6 hours after transfusion. In general, this is a benign adverse event.
Bacterial infection	Blood components are excellent media for bacteria to grow. Contamination can occur after collection or storage of blood. There is a higher risk with platelet transfusions. The risk for severe bacterial infections and sepsis is around one in 50,000 platelet transfusions and one in 500,000 blood transfusions.
Acute hemolytic reaction	This reaction may constitute a real medical emergency. It can occur just a few minutes after a transfusion. It entails fast destruction (hemolysis) of donor RBCs by recipient antibodies. The most common cause is human error. Hemolytic symptoms include chills, headache, backache, dyspnea, cyanosis, chest pain, tachycardia, and hypotension. It can lead to acute renal failure.
Anaphylactic reaction	An anaphylactic reaction can occur at a rate of one per 30,000–50,000 transfusions. These reactions are most commonly seen in people with selective IgA deficiency. An anaphylactic reaction is a medical emergency, and may be life-threatening.
TRALI	TRALI is a syndrome of acute respiratory distress, often associated with fever, noncardiogenic pulmonary edema, and hypotension. It may occur as often as 1 in 2,000 transfusions. Symptoms range from mild to life-threatening, but most patients recover fully within 96 hours of the event. Mortality rate is <10%.
Volume overload	Patients with impaired cardiac function can become volume overloaded as a result of blood transfusion, leading to edema, dyspnea, and orthopnea.
Iron overload	Each transfused unit of RBCs contains approximately 250 mg of elemental iron. Because elimination pathways for iron are limited, a person receiving numerous RBC transfusions can develop iron overload. The threshold at which iron overload becomes significant is somewhat unclear, but is likely around 15–20 units of RBCs transfused.
Delayed hemolytic reaction	It occurs 6–10 days after transfusion. It may vary from mild to severe. Symptoms include fever and unexpected low hemoglobin with jaundice. It can occur at a rate >1:10,000.
Transfusion-associated GVHD	GVHD: an immune attack by the transfused cells against the recipient. Common complication in the stem cell transplantation setting. Extremely rare after a routine blood transfusion. It occurs only in immunocompromised patients. When it occurs it is almost always fatal. This event can be eliminated by irradiation of the blood prior to transfusion.
Post-transfusional purpura	Thrombocytopenia occurs 6–10 days after an RBC transfusion. Most patients are women and all have been previously pregnant (several pregnancies) or transfused. Patients have a complement-fixing antiplatelet antibody in their serum against PIA1. Patients' platelets lack PIA1 (97% of the population have PIA1).

Abbreviations: GVHD, graft-versus-host disease; TRALI, transfusion-associated acute lung injury.

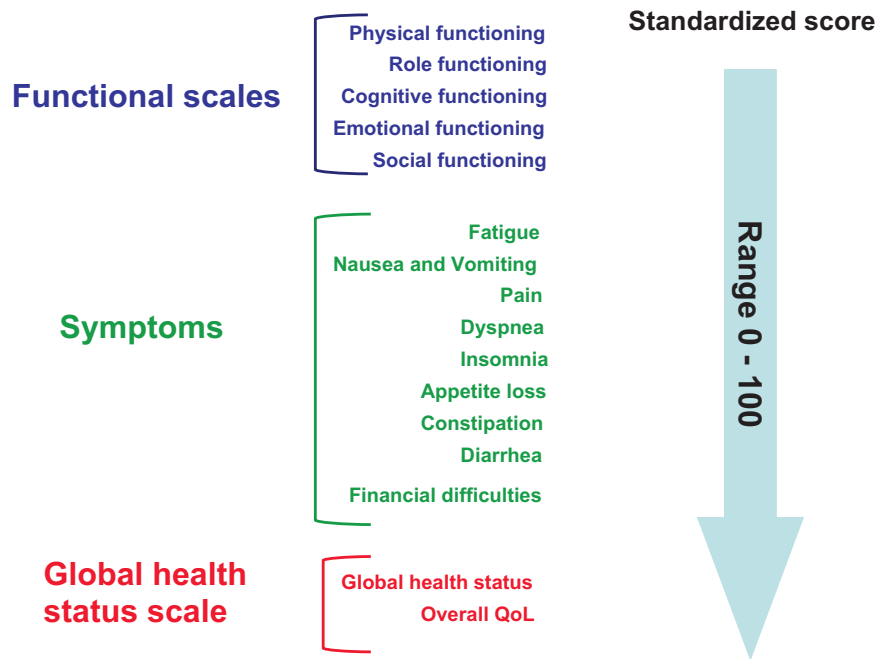


Figure 6. Overview of aspects included in the European Organization for Research and Treatment of Cancer core quality of life (QoL) measurements.

fusion-related mortality, but it is possible that a new transfusion-transmitted agent could emerge in the future, causing a fatal infectious disease [63]. Interestingly, randomized controlled trials comparing cardiac surgery patients receiving non-WBC-reduced blood components with patients receiving WBC-reduced blood components showed greater mortality associated with the use of non-WBC-reduced ABT [63].

Nowadays, the risk of dying after a blood transfusion is low, and if a death did occur the most probable cause would be either human error or an accident. So, although our blood banks and blood transfusions are relatively safe, they need to be used with caution because they can cause complications. Furthermore, our blood supply does remain vulnerable to as yet unknown potentially lethal viruses and other pathogens.

QoL: IMPACT OF ANEMIA AND ESAS

QoL is multidimensional, and measurements of QoL must capture patients' physical functioning, social functioning, and emotional functioning. There are various instruments available for measuring QoL, such as the European Organization for Research and Treatment of Cancer (EORTC) QoL 30, the Contentment with Life Assessment Scale (CLAS), the Functional Assessment of Cancer Therapy–Fatigue (FACT-F), the FACT–Anemia (FACT-An), and the Short Form 36. The EORTC core QoL instrument includes functional scales and also measures symptoms and global health status (Fig. 6).

Impact of Anemia on QoL in Cancer Patients

Anemia impairs QoL in cancer patients. In a study of MDS patients with anemia, QoL scores were significantly lower in MDS patients than in the gender- and age-matched reference population [37]. In anemic patients with an Hb level <10 g/dl, fatigue and dyspnea were significantly more prominent than in the control group [37].

Fatigue is common in patients receiving chemotherapy. In patients with chemotherapy-induced anemia, more than two thirds (76%) of patients experience fatigue at least once in 4 weeks [63]. A subset of these patients (24%–32%) experience fatigue daily [62]. Decreased Hb level and increased fatigue results in reduced QoL. A low Hb level is also associated with more symptoms [64, 65]. Cancer patients with Hb levels <12 g/dl have significantly more fatigue, greater nonfatigue anemia symptoms, poorer physical well-being, poorer functional well-being, and lower general QoL [65].

Demetri et al. [66] measured the relationship between changes in QoL and changes in Hb level in cancer patients during treatment with EPO. When the Hb level decreased, patients with progressive disease had the greatest decrease in QoL ($p < .05$) [66]. When the Hb level increased by 0–2 g/dl, QoL significantly improved for responding patients, but QoL was still significantly lower than baseline for patients with progressive disease ($p < .01$) [66]. When the Hb level increased by ≥ 2 g/dl, improvement in QoL in all patient groups was seen, and in particular in patients with progressive disease ($p < .05$) [66].

Cancer and renal patients experience similar changes in QoL [67]. There is a close correlation between QoL and change in Hb level [67]. An increasing hematocrit or Hb level improves the well-being of both cancer and renal disease patients [67].

In the Cardiovascular risk reduction by early anemia treatment (CREATE) study, anemic renal insufficiency patients were treated with ESAs [68]. Patients who achieved a target Hb in the normal range (13.0–15.0 g/dl) showed a significant improvement in QoL, compared with those who didn't achieve the treatment goal (i.e., Hb level, 10.5–11.5 g/dl) [68].

QoL Associated with ESAs

ESAs improve fatigue and energy rating scores in cancer patients with chemotherapy-induced anemia. In anemic patients receiving chemotherapy for nonmyeloid malignancies, the FACT-F subscale score increased by a mean of 26%, and improvements in fatigue paralleled the observed increases in Hb level [69].

It does need to be acknowledged that fatigue can also be a result of other compounding factors, such as infection, hormone imbalance, etc.

In cancer patients, overall QoL significantly improved in patients receiving epoetin alfa treatment, compared with the placebo group [18, 70]. In the Littlewood et al. [18] study, the changes in FACT-General, FACT-An:Fatigue, and FACT-An:Anemia scores from baseline to last assessment were significantly better for the ESA group than for the placebo group ($p < .05$, $p < .01$, and $p < .01$, respectively).

A meta-analysis of prospective randomized trials with patients treated with epoetin alfa ($n = 11,459$) looked systematically at QoL issues and found a correlation between epoetin alfa treatment and improvements in FACT and CLAS scores [71]. There were significant improvements in the mean change from baseline FACT scores in patients receiving epoetin alfa, compared with control patients [71]. Improvement from baseline for three CLAS subscales was significantly better ($p < .05$) and substantial (20%–25%) in patients receiving epoetin alfa compared with control patients [71].

Several meta-analyses looked at subsets of studies that had included QoL assessments. These meta-analyses showed an improvement in QoL in patients receiving ESA treatment [19, 72–75]. In the Bohlius et al. [19] qualitative meta-analysis, 14 of 27 randomized controlled trials (RCTs) reported changes in symptoms of QoL and eight trials showed a significant improvement in QoL for ESA-treated patients. In the Minton et al. [72] quantitative meta-analysis, 27 RCTs of epoetin alfa and darbepoetin alfa

looked at changes in fatigue using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue subscale. The overall self-reported fatigue effect of epoetin alfa over control was $Z = 8.32$ ($p < .001$) and of darbepoetin alfa over control was $Z = 1.45$ ($p = .05$) (where the Z -value denotes the improvement over the mean) [72]. The weighted mean difference in change (MDIC) in FACIT-Fatigue (epoetin alfa plus darbepoetin alfa) versus control was 3.75 (MDIC of FACIT-Fatigue, 3.0) [72]. The qualitative meta-analysis of Seidenfeld et al. [73] (involving 59 trials of epoetin alfa, darbepoetin alfa, or both) showed, overall, QoL measures (including self-reported fatigue) favoring ESA treatment (15 studies). The quantitative meta-analysis of Ross et al. [74] (involving 40 studies of epoetin alfa and darbepoetin alfa), looking at self-reported fatigue (FACIT-Fatigue or Linear Analogue Self-Assessment [LASA]) outcomes, showed a small, but significant, improvement in fatigue in ESA-treated patients versus control patients—ESA, 0.23 ($p < .01$) (FACIT-Fatigue); ESA, 0.36 ($p < .01$) (LASA). The qualitative meta-analysis of Kimel et al. [75] (with nine RCTs of epoetin alfa) included self-reported fatigue (FACIT-Fatigue) and QoL (LASA) outcomes. FACIT-Fatigue change scores and LASA change scores (energy, daily activities, overall QoL) favored the ESA arms in all trials [75].

A systematic review of all randomized controlled trials in which ESA treatment was given and QoL data were collected involved 40 studies including 21,378 patients (epoetin alfa or darbepoetin alfa versus control) [74]. Patients receiving ESAs experienced a significant improvement in QoL, regardless of the QoL instrument used [74]. The mean difference in FACT-F score for ESA versus control was 0.23 (95% CI, 0.10–0.36; $p = .001$) [74].

Figure 7 shows the relationship between improvement in Hb and improvement in QoL [42, 76]. The greatest gain in QoL was obtained when the Hb level rose from 11 g/dl to 12 g/dl [42, 76]. There was some further improvement in QoL when the Hb level increased to 12 g/dl and 14 g/dl; however, the gain then leveled off [42, 76].

There is a relationship among transfusion, QoL (in terms of fatigue), and Hb level [77]. When patients present with a low Hb level at the start of treatment, the probability of having a transfusion is high (about 50%, based on repeated measures likelihood ratio modeling) [77]. When the Hb level increases to normal or the target of 12 g/dl, the probability of requiring a transfusion is reduced to zero [77–81]. Concomitantly, the FACT-F score increases with increasing Hb level. Therefore, not only is there a gain in reducing the number of transfusions to zero but there is also a steep and continuous increase in the fatigue score when the Hb level increases.

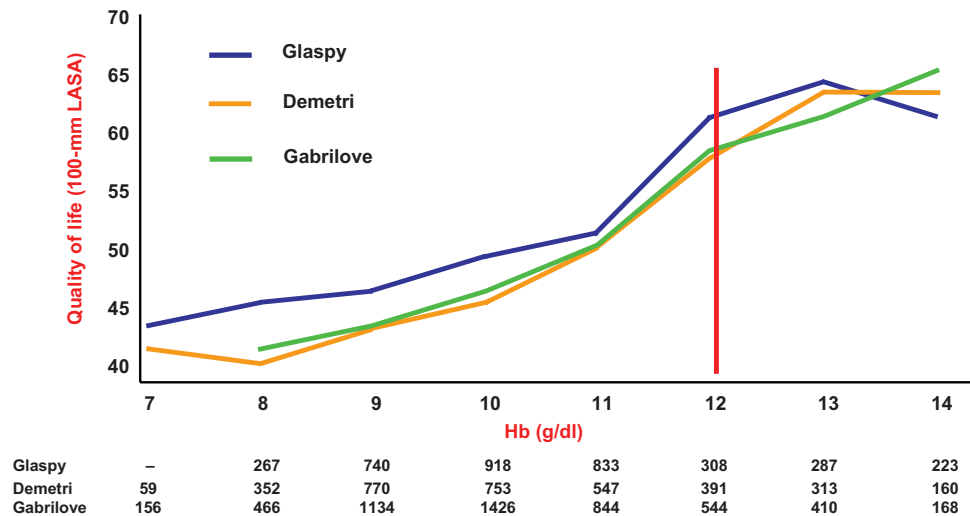


Figure 7. Epoetin alfa phase IV studies in tumor-associated anemia: Incremental increase in quality of life and hemoglobin (Hb) level [42, 66, 76].

Abbreviation: LASA, Linear Analogue Self-Assessment.

In the past, QoL was neglected because of a lack of appropriate interventions. The introduction of ESAs provided therapeutic changes that were related to QoL, with ESAs enhancing QoL. General and specific instruments were developed that were measurable and validated. QoL measurements showed the impact of treatment interventions. Several studies proved the positive impact of ESAs on QoL, showing that ESAs increase the Hb level, resulting in a lower number of transfusions and better QoL. These findings are rewarding and motivate oncologists and hematologists to continue providing appropriate treatments for anemic patients undergoing cancer therapy.

CONCLUSIONS

Recombinant EPOs are effective in alleviating anemia, diminishing transfusion use, and improving QoL in anemic cancer patients receiving chemotherapy. Because the Hb level is not an accurate surrogate for the RBC mass in cancer patients, it should not be raised higher than 12 g/dl. ESAs have proven to be safe at this Hb level. There is at present no indication for recombinant EPO in the treatment of anemia of cancer in the absence of chemotherapy. There

is a possibility of a higher incidence of TE events with ESAs, and the overall benefit–risk ratio must be considered on an individual patient basis, while also taking into account the impact on the patient’s QoL. Recombinant EPO induces inflammatory cytokine production and contracts the plasma volume, and high doses of recombinant EPO may be more likely to produce these effects. Therefore, three times weekly injections may be more physiologic than a single large weekly injection. Recombinant EPO should also not be given in proximity to blood transfusions. Thrombocytosis should be considered as a marker of an inflammatory state and a predisposition to thrombosis when an ESA is being given.

AUTHOR CONTRIBUTIONS

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