Chapter 8

Anemia and Cancer

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Introduction

This chapter explores the management of anemia in older cancer patients. Cancer is a disease of aging: more than 50% of all malignancies currently occur in the 12% of the population aged 65 and over; by the year 2030 older individuals are expected to account for 20% of the population and 70% of all cancer cases (1). Though not unique of older individuals, anemia is a common manifestation of cancer, especially of advanced cancer (2). The elderly are expected to suffer disproportionately of cancer-related anemia, because cancer becomes more common with age and because age itself is a risk factor for anemia (1–3).

Anemia is detrimental to cancer patients, because it compromises patient well-being, and it may increase the complications and reduce the benefits of antineoplastic treatment (2). Anemia of chronic inflammation (ACI) and of chemotherapy are the most common forms of anemia in cancer patients and both respond to pharmacological doses of erythropoietin (2, 4). The availability of a number of synthetic erythropoiesis-stimulating factors (ESF) that mimic the action of erythropoietin has allowed the correction of anemia in the majority of cancer patients.

After reviewing the pathogenesis of anemia we will examine the consequences of anemia for the older cancer patients and the benefits and potential risks of treatment with ESF.

Causes and Mechanisms of Anemia in the Cancer Patient

Table 8.1 lists common causes of anemia in patients with cancer. Anemia of chronic inflammation is the most common form of anemia in cancer patients and in older individuals, as aging is a form of chronic and
progressive inflammation (3, 5, 6). Central to the pathogenesis of this form of anemia is a “relative erythropoietin deficiency” that involves inadequate production of erythropoietin for the degree of anemia, and increased resistance of erythropoietic precursors to erythropoietin (7–9). Undoubtedly, in older individuals, some degree of renal insufficiency may be responsible for the reduced erythropoietin response to anemia, as the glomerular filtration rate declines almost universally after age 65 (10). Increased concentration of circulating inflammatory cytokines, such as interleukin-6 (IL-6) or tumor necrosis factor (TNF) may blunt erythropoietin production as well as the sensitivity of the erythropoietic progenitors to erythropoietin (3) (Fig. 8.1). In older individuals, Ferrucci et al. (9) showed a biphasic effect of inflammatory cytokines on erythropoietin production: in the absence of anemia, increased concentration of inflammatory cytokines was associated with increased concentration of erythropoietin, and in the presence of anemia, with reduced erythropoietin concentration. Similar findings were reported by Ershler et al. (8) in older individuals followed in the Baltimore Longitudinal Study. The authors hypothesized that inflammatory cytokines initially stimulate the secretion of erythropoietin, and that eventually, due to the continuous stimulation, the ability of the organism to produce erythropoietin becomes exhausted. This hypothesis is supported by experimental observations that IL-6 stimulates the kidney secretion of erythropoietin (11). The higher levels of erythropoietin seen in nonanemic individuals may fail to rise the hemoglobin concentration to supra-normal levels, as the sensitivity of

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<tr>
<th>Table 8.1. Causes of anemia in cancer patients</th>
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<tr>
<td><strong>Common causes</strong></td>
</tr>
<tr>
<td>• Anemia of chronic inflammation (ACI)</td>
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<tr>
<td>• Chemotherapy-induced myelosuppression</td>
</tr>
<tr>
<td>• Iron deficiency</td>
</tr>
<tr>
<td>• Myelophthisis</td>
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<tr>
<td><strong>Other important causes</strong></td>
</tr>
<tr>
<td>• Cobalamine deficiency</td>
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<tr>
<td>• Renal insufficiency</td>
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<tr>
<td>• Folate deficiency</td>
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<tr>
<td>• Autoimmune hemolytic anemia</td>
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<td>• Microangiopathic anemia</td>
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erythropoietic progenitors to erythropoietin is blunted by the same inflammatory cytokines. Another consequence of chronic inflammation and more specifically of increased concentration of IL-6, is the increased hepatic production of hepcidin, a glycoprotein that prevents the mobilization of iron from the deposits as well as the intestinal absorption of iron (12). This fact explains while some cancer patients fail to increase their hemoglobin in response to erythropoietin, unless they are supplemented also with iron intravenously (13).

ACI is usually normochromic, normocytic but can, less commonly, be mildly hypochromic, and microcytic and typically is associated with low concentrations of iron, total iron binding capacity and soluble transferrin receptor (sTfR) in the circulation and increased levels of ferritin (4). The erythropoietin levels are variable but in general lower than those observed in iron deficiency for the same hemoglobin levels.

Chemotherapy-related anemia is hypoproliferative, macrocytic, and megaloblastic, and is due to the inhibition of DNA synthesis in erythropoietic precursors (2). Due to the concomitant presence of cancer, the majority of patients receiving cytotoxic chemotherapy also experience ACI, responsive to erythropoietin treatment.

The causes of iron deficiency in cancer patients include bleeding from cancer of the digestive tract and the endometrium, and bleeding from benign causes, such as diverticular disease of the colon, angiodysplasia, or polyps, all of which become more common with age.

Fig. 8.1. Pathogenesis of anemia of Chronic Inflammation
*Helicobacter pylori* gastritis may also lead to iron deficiency as the microorganism utilizes the iron as a nutrient for its own growth, but the prevalence of this condition is unknown. It is reasonable, albeit not conclusively proven, to assume that some cases of iron deficiency in elderly individuals are nutritional, when a cause for iron loss is not found (14). Gastric atrophy may prevent the reduction of food-bound iron necessary for its absorption, and hepcidin may also hinder the absorption of iron (13). In its classical form iron-deficiency anemia is hypoproliferative, microcytic, and hypochromic, and is characterized by low circulating levels of iron and ferritin and increased levels of sTfR and total iron binding capacity (4).

The prevalence of cobalamin deficiency may be as high as 15% among individuals over 60 (15), due to failure to digest food-bound vitamin B12, which results from gastric atrophy. Oral cobalamin preparations may correct the deficiency in these patients (16). It should be emphasized that as many as 15% of patients with serum vitamin B12 levels between 180 and 300 pg/mL, which are considered normal, have functional vitamin B12 deficiency, as shown by increased circulating levels of methylmalonic acid and homocysteine (15–18). Unless it is associated with folate deficiency, cobalamin deficiency may not lead to anemia and its first manifestations in this case are neurological, including posterior column degeneration, peripheral neuropathy, and dementia (16).

Folate deficiency is common in patients with decreased food intake, including those with cancer of the head and neck and may be found among elderly individuals with low intake of leafy vegetables (17, 18). Though more common in hematologic malignancies, myelophthisis may be observed in patients with solid tumors metastatic to the bones, especially breast cancer, prostate cancer, and small cell lung cancer. Myelophthisis may present as pancytopenia with an increased concentration of immature blood cells in the circulation (21).

Sarcopenia, a common manifestation both of cancer (22) and of frailty, may also contribute to the pathogenesis of anemia in older cancer patients, with reduced synthesis of proteins, including hemoglobin and erythropoietin (23).

Perhaps in the majority of cases the anemia of cancer is multifactorial and includes chronic inflammation, chemotherapy, and malnutrition. Correctable causes of anemia, including iron, folate, and cobalamin deficiency, hypothyroidism, and chronic renal disease should be investigated and managed. ESF are the mainstay of the management of ACI and chemotherapy-related anemia (2).
Complications of Anemia in Cancer Patients

The complications of anemia in the older cancer patient may include

- **Fatigue and functional dependence.** Fatigue is a feeling of tiredness unrelated to physical activity and not relieved by rest (24). It is the most common chronic symptom both of cancer and of chemotherapy, and is associated with serious consequences in the life of the patient and his/her caregivers, including reduction of working hours and even inability to work. Approximately 40% of cancer patients and 20% of their caregivers had to quit working or take leave from work because of the patient’s fatigue (24). Fatigue is clearly related to anemia: correction of anemia relieves the fatigue of the majority of cancer patients and improves their quality of life (2). In older patients, anemia is also associated with increased risk of functional dependence, that is need of external help to carry on the basic activities of daily living (ADL) or the instrumental activities of daily living (IADL) (25–29). In older cancer patients fatigue is associated with functional dependence (30).

- **Chemotherapy-induced toxicity.** Anemia has been associated with increased risk of chemotherapy-induced toxicity (31–35). Anemia has a two-fold pharmacodynamic effect. Through hypoxia it may make normal tissues more susceptible to injury. In addition, anemia leads to a shrinkage of the volume of distribution of hydrosoluble agents, that are bound to red blood cells. In the presence of anemia the free concentration of these compounds in the circulation, and the risk of complications, may increase.

- **Reduced response to radiation therapy.** The response to radiotherapy of cancer of the upper airways, upper digestive tract, and the cervix was lower in anemic than nonanemic patients (2). Resistance to radiation therapy seemingly was mediated by tumor hypoxia, that prevented the formation of free radicals capable to damage the tumor DNA.

- **Impaired cognitive function.** Several lines of evidence indicate that anemia is associated with compromised cognitive function. In patients with end-stage renal failure, correction of anemia with ESF was associated with reduced incidence of dementia (36). Several studies reported higher prevalence of cognitive compromise among anemic than nonanemic elderly (37, 38). In a cohort study, Atti et al. (39) reported that anemia heralded the development of dementia over 3 years for individuals who were not demented (39). Likewise, the development of cognitive deficits in the course of adjuvant chemotherapy of breast cancer was more common in anemic patients (40).
Blood transfusion dependence and its associated risks. Blood transfusions clearly serve a role in the management of severe anemia. Symptoms such as dyspnea on mild exercise or angina in patients with coronary artery disease respond promptly to blood transfusion. This treatment is associated with some risks, including transfusion-transmitted infections, transfusion reactions, transfusion-related immunomodulation (TRIM) with increased risk of tumor recurrence, and platelet refractoriness (41). Thanks to improvements in donor history questions and infectious disease marker testing, the risk of infections has been substantially reduced. Minor transfusion reactions, including urticaria and febrile nonhemolytic transfusion reactions, occur in about 0.5–1.0% of all transfusions, and while not harmful, can cause concern since they can mimic more serious reactions (41). TRIM has been deemed responsible for the poorer outcomes experienced by transfused patients as compared to those who had not been transfused (42). HLA and RBC alloimmunization is the consequence of multiple blood transfusions and may lead to delayed hemolytic reactions and to refractoriness to transfused platelets (43).

Adverse effects on longevity. According to at least seven cohort studies (29, 44–49) anemia is an independent risk factor for mortality in individuals 65 and older, which represent 50% of all cancer patients (1).

Given the deleterious effects of anemia, and of blood transfusions, the ESF have represented a welcome addition to the management of anemia in older cancer patients. The effectiveness and risks of these compounds have been explored in a number of clinical trials.

Commercial Preparations of Erythropoietic Growth Factors

Currently available ESF include epoetin α, epoetin β (available only in Europe), and darbepoetin α (2). Darbepoetin α differs from epoetin α by the inclusion of glycosyl residues that prolong the half-life of the compound. Epoetin needs to be administered weekly, whereas darbepoetin may be administered every 3 weeks (50, 51). The activity of epoetin and darbepoetin appear similar and the main advantage of darbepoetin is less frequent administration.

Other erythropoietic stimulators are undergoing clinical trials. The CERA (Continuous Erythropoietin Receptor Activator), is a molecule of epoetin with a polymeric side chain that prolongs its half-life of several weeks (52) and may require less frequent administration than darbepoetin. A completely synthetic erythropoietic stimulator, Hematide, has been prepared and is undergoing early clinical experimentation (53).
Effectiveness and Risk of ESF in Cancer-Related Anemia

**Trial designs.** The management of the older cancer patients with ESF has been studied in three types of trials (2):

- Single arm trials in anemic patients aimed to establish whether improvement in hemoglobin resulted in reduction of blood transfusions and improvement in energy. The treatment was discontinued for hemoglobin levels around 12 g/dL.
- Randomized controlled trials in anemic patients aimed to establish whether improvement of hemoglobin was associated with better survival and response to chemotherapy in addition to improvement in quality of life and reduction in blood transfusions. In most of these trials ESF were discontinued for hemoglobin levels of 12 g/dL.
- Randomized controlled studies in anemic and nonanemic patients aimed to achieve and maintain normal hemoglobin levels, on the assumption that normal hemoglobin levels would have been beneficial both in terms of function, quality of life, treatment tolerance, and survival.

**Effectiveness of the Treatment.** We will address the benefits of ESF for each complication of anemia.

**Fatigue.** Treatment with epoetin α improved the anemia in 50–60% of patients with solid tumors who were followed longitudinally (54–56). The improvement in hemoglobin levels was associated with improved energy levels and quality of life and reduced incidence duration and severity of fatigue, irrespective of the status of the tumor. In other words, improvement of hemoglobin was beneficial to the quality of life of all patients, including those whose cancer had progressed. The maximal incremental improvement in energy was obtained when hemoglobin levels increased from 11 to 13 g/dL (24). These results were confirmed in subsequent randomized controlled studies (2, 57, 58).

**Blood transfusions.** Reduction of blood transfusions, thanks to ESF, was demonstrated in all randomized controlled studies. The average reduction in blood transfusions was approximately 30% (58).

**Response to treatment and overall outcome.** Treatment with ESF failed to improve survival, response to treatment, or chemotherapy-related toxicity in each of the randomized controlled studies. Patients enrolled in these studies had different types of tumors, at different stages and received different forms of treatment, so that it is difficult to draw definite conclusions related to survival (58).

**Risk of functional dependence.** This outcome is particularly relevant to older patients, for whom functional dependence is more common and more
likely irreversible. One may infer a benefit of functional dependence from two studies. The Fatigue Coalition reported that fatigue was detrimental to the function of the patient and the caregiver (24). A decision analysis calculated that the cost of caring for older individuals was increased by anemia and the management of anemia with recombinant erythropoietin was cost-effective in these individuals (59).

Treatment complications. Three types of complications have been reported: autoimmune aplastic anemia (secondary to anti-erythropoietin antibodies), cardiovascular complications (including hypertension, venous, and arterial thrombosis), and increased rate of tumor growth.

Autoimmune aplastic anemia. This complication was described in 175 patients treated with epoetin α and β for anemia of chronic renal failure (60), was never reported in cancer patients, occurred exclusively in Europe, and appeared to be a manufacturing-related problem. Since standardized rules for preparation and handling of epoetin have been established, the incidence of this complication has decreased by 83%.

Cardiovascular complications. Concern about these complications, that have been well documented, prompted an Oncology Drug Advisory Committee (ODAC) conference involving all companies that produced recombinant erythropoietin (http://www.FDA.gov/ohrms/dockets/ac/04/slides/4037s2.htm). The conclusion of the conference participants was that the majority of these complications occurred in studies aimed to maintain normal levels of erythropoietin in cancer patients or in studies trying to increase the levels of erythropoietin too rapidly. As long as the currently recommended doses of erythropoietin were maintained and the treatment did not aim to levels of hemoglobin higher than 12 g/dL the treatment appeared safe and no special warning was needed.

Increased rate of tumor growth. The possibility of enhanced tumor growth was suggested in two published studies (61, 62), one in patients with cancer of the head and neck (61) and the other in patients with breast cancer (62) and was suggested in seven other studies reviewed by the ODAC conference. A recent meta-analysis of randomized controlled studies of ESF suggested a minor detrimental effect of these factors on survival (58). Definitive conclusions related to the risk of enhanced tumor growth could not be reached at the ODAC conference. The conference participants agreed that the overall risk, if present at all, was small enough that it did not erase the benefits of treatment. Also enhanced tumor growth appeared more prominent in studies aimed to maintain normal hemoglobin levels, but was negligible when hemoglobin levels were maintained around 12 g/dL.

An analysis of patients with head and neck cancer might have provided a clue to the potential risk of ESF in these patients (63). Some of the
tumors, which were rich in erythropoietin receptors, experienced accelerated growth during treatment with ESF, whereas tumors poor in receptors did not experience growth stimulation. If this observation is confirmed, determination of erythropoietin receptors on the tumor may help select patients for ESF treatment.

Practical Issues Related to the Treatment with ESF

Which patients should be treated. According to the ASCO and NCCN guidelines (Table 8.2) (64) treatment should be initiated in all patients whose level of hemoglobin is lower than 10 g/dL. For hemoglobin levels between 10 and 12 g/dL the treatment should be initiated if the patient is symptomatic. In light of current knowledge these recommendations appear very reasonable and safe.

Table 8.2. Recommendation for treatment with epoetin in cancer patients

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<tr>
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<th>ASCO</th>
<th>NCCN</th>
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<tr>
<td>Indications for starting treatment</td>
<td>Hb &lt; 10 g/dL</td>
<td>&lt;11 g/dL</td>
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<tr>
<td></td>
<td>Hb &lt; 12 g/dL in</td>
<td></td>
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<tr>
<td></td>
<td>symptomatic patients</td>
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<tr>
<td>Response</td>
<td>Hb:1–2 g/dL</td>
<td>Hb:1 g/dL</td>
</tr>
<tr>
<td>Dose increment</td>
<td>No response 6–8 weeks</td>
<td>No response 8–12 weeks</td>
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<tr>
<td>Duration of treatment with increased dose</td>
<td>4–8 weeks</td>
<td>4–8 weeks</td>
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<tr>
<td>Discontinuance</td>
<td>No response after treatment with increased dose</td>
<td>No response after treatment with increased dose</td>
</tr>
<tr>
<td>Objective 12 g/dL</td>
<td>Hb: 12 g/dL</td>
<td>Hb:12 g/dL</td>
</tr>
<tr>
<td>Maintenance</td>
<td>D/C after reaching the objective or titrate dose to maintain Hb levels @ 12 g/dL</td>
<td>Titrate dose to maintain Hb levels @ 12 g/dL</td>
</tr>
<tr>
<td>Iron supplementation</td>
<td>No specific indication except for clear evidence of iron deficiency</td>
<td>Iron deficiency</td>
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When it is reasonable to stop the treatment? Generally it is recommended that treatment be discontinued for hemoglobin levels \( \geq 12 \, \text{g/dL} \). The increment in energy is lower when the hemoglobin rises above these levels and the risk of treatment complications increases.

What are the optimal doses? Common doses are 40,000 IU weekly for epoetin \( \alpha \) and 300 \( \mu \text{g/kg} \) every 3 weeks for darbepoietin \( \alpha \). If after a month of treatment an increase in hemoglobin levels of at least 1 g/dL is not observed doses should be increased to 60,000 IU or 500 \( \mu \text{g/kg} \), respectively. If no erythropoietic response is observed with these doses after 1 month, the treatment should be discontinued. Once hemoglobin levels \( \geq 12 \, \text{g/dL} \) are obtained, maintenance treatment with reduced doses may be instituted. According to recent studies epoetin \( \alpha \) may be effective at doses of 120,000 units every 3 weeks (65).

Should iron be administered together with erythropoietic growth factors? Iron deficiency should be corrected before therapy with recombinant erythropoietin. In patients with normal or increased iron stores, the addition of iron may be beneficial. A recent study randomized patients with cancer and chemotherapy-related anemia to receive no iron, oral iron, or intravenous iron (11). Whereas oral iron had no effect, intravenous iron was associated with a doubling of the erythropoietic response rate.

Erythropoietic Growth Factors and Red Blood Cell Transfusions: Effectiveness, Safety, and Cost Considerations

Red blood cell (RBC) transfusions have been the mainstay treatment of anemia until the introduction of ESF. The indications for RBC transfusions have been the treatment of symptomatic anemia. Patients commonly require blood transfusion when hemoglobin drops <7 or <8 g/dL or <10 g/dL when significant coexisting cardiac, pulmonary or vascular disease is present.

- The major advantage of erythropoietin over blood transfusions has been the maintenance of consistent hemoglobin levels, which resulted in consistent levels of energy and might have prevented life-threatening complications of anemia. When used according the ASCO and NCCN guidelines, erythropoietic growth factors appear safer than blood transfusions. Cremieux et al. (66) calculated that the monthly cost of treating a patient with epoetin \( \alpha \) was similar to the cost of two monthly RBC transfusions. As only a fraction of patients treated with ESF would need two monthly blood transfusions according to the guidelines, it is clear that ESF increase the overall cost of cancer treatment.
This cost may be worthwhile when one considers the impact of fatigue on the indirect and intangible cost of managing cancer patients (67). This cost is particularly high for older individuals who are more susceptible to experience functional dependence as a consequence of anemia and fatigue.

Conclusions

In conclusion:

- In cancer patients anemia is responsible for fatigue and lower quality of life, poor therapeutic response, increased risk of chemotherapy related toxicity, and increased use of blood transfusions.
- In older individuals, anemia has been associated with reduced longevity, dementia, depression, and functional dependence.
- Correction of anemia with ESF has improved the function and quality of life of cancer patients, irrespective of their age, and reduced the use of blood transfusions.
- ESF appear safe when hemoglobin levels are maintained around 12 g/dL.
- Though costly, treatment with ESF appears to reduce the indirect and intangible cost of managing older patients with cancer.

References


