Cancer-Related Anemia: Special Considerations in the Elderly

Anemia raises special concerns in older cancer patients. This review addresses the prevalence, causes, and mechanisms of anemia in older individuals, the complications of anemia in this population (including its impact on cancer treatment), and the appropriate management of anemia in the elderly.

A common manifestation of cancer, anemia may compromise patient welfare and influence treatment outcome.[1] In older cancer patients, anemia raises special concerns for the following reasons:

- The incidence and prevalence of cancer increase with age.[2]
- The incidence and prevalence of anemia increase with age.[3,4]
- Anemia—even mild anemia—is associated with a number of unfavorable outcomes in older individuals.[5]

This article explores the causes, consequences, and management of anemia in older individuals, and the influence of anemia on cancer treatment.

Prevalence, Causes, and Mechanisms

Definition of Anemia

According to the World Health Organization (WHO), anemia is defined as hemoglobin levels lower than 12 g/dL in women and 13 g/dL in men.[2] Recent findings have called into question this definition, which nevertheless remains the gold standard for epidemiologic and clinical studies, as well as for clinical practice.

A critical issue concerns whether it is justified to use different normal values for postmenopausal women and men. The Women's Health and Aging Study (WHAS) followed 667 home-dwelling women aged 65 and older for 11 years and established that hemoglobin values lower than 13 g/dL were an independent risk factor for mortality and disability.[6,7] Similar results were reported from the Invecchiare in Chianti (InChianti) study, a cross-sectional look at the older population in the Italian region of Chianti.[8] In addition, several years ago, the fatigue coalition reported that the highest increment in energy, both in men and women with cancer, was obtained when hemoglobin levels were raised from 11 to 13 g/dL, suggesting that hemoglobin levels around 13 g/dL may be optimal for both sexes, at least in the later years of life.[9]

Another problem with the WHO definition is its failure to account for ethnicity. In the United States, the National Health and Nutrition Examination Survey (NHANES) III confirmed previous reports that hemoglobin levels in healthy African-Americans may be lower than in Caucasians.[2] It has not been established whether a higher prevalence of hemoglobinopathies among African-Americans is responsible for this difference.

Individual variations in hemoglobin levels may also be present irrespective of ethnicity and sex. While hemoglobin levels lower than 12 g/dL are probably abnormal for everybody, it is possible that levels between 12 and 13 g/dL are abnormal for some women and men and normal for others. In the following discussion, we will use the WHO definition as reference, recognizing that it may lead to underdiagnosis of anemia and its causes especially in older women.

Incidence and Prevalence of Anemia

Incidence and prevalence of anemia increase with age[3,4] and are highest in the institutionalized population.[4,10-12] According to cross-sectional studies, average hemoglobin levels remain constant throughout all age groups at least up to age 90.[13] Anemia appears not to be a consequence of aging, but the incidence and prevalence of chronic diseases causing anemia increase with age.

In the NHANES III study, anemia was more common among women up to age 50, was equally prevalent in the two sexes up to age 65, and became more common in men after age 65.[3] This finding is dependent on the definition of anemia. If the lower-normal levels of hemoglobin in women were set at 13 g/dL instead of 12 g/dL, incidence and prevalence of anemia would be higher in women throughout the age spectrum.

Causes and Mechanism of Anemia
Common causes of anemia in older individuals are reported in Table 1.[3,14,15] In all reviews, so-called "idiopathic anemia" accounted for 15% to 30% of cases. Undoubtedly some of these cases were due to inadequate investigations and might have involved early myelodysplasia[16] or early renal insufficiency, whose incidence increases with age.[17,18] In some cases, a condition called "relative erythropoietin insufficiency" might have been present. Several investigators have found circulating levels of erythropoietin to be more elevated in older individuals than in their younger counterparts for hemoglobin levels ≥ 12 g/dL.[19,20] For hemoglobin < 12 g/dL, the levels of erythropoietin were lower in the older individuals (Figure 1). These data suggest that:
• The erythropoietic precursors become resistant to erythropoietin with aging. Thus, higher levels of erythropoietin are needed to maintain a normal hemoglobin level. It is also possible that reduced capillary blood flow causes tissue hypoxia, which is responsible for elevating erythropoietin levels to achieve a normal hemoglobin count.
• The ability to produce erythropoietin declines with age, and the erythropoietin response to anemia is inadequate in older individuals. Declining renal function may account in part for this inadequacy. Other mechanisms may include increased circulating levels of inflammatory cytokines and exhaustion of the ability to produce erythropoietin.

The pathogenesis of this type of anemia is interwoven with the pathogenesis of anemia of chronic inflammation (ACI), in which relative erythropoietin deficiency has been repeatedly described. Aging is a form of chronic and progressive inflammation, and the concentration of circulating inflammatory cytokines that inhibit erythropoiesis increases with age. Among these, interleukin (IL)-6, IL-2, interferon-gamma, and tumor necrosis factor (TNF) are known to modulate the production of erythropoietin and to reduce the sensitivity of the erythropoietic progenitors to erythropoietin. The idiopathic anemia that one finds in older individuals may just represent a form of ACI. Another important characteristic of ACI is reduced mobilization of iron from stores. Hepcidin, a protein whose hepatic production is enhanced by IL-6, is responsible for reduced mobilization of iron and impaired absorption of this element from the intestine, which explains why patients with ACI have a better response to erythropoietin when provided with intravenous iron.
Iron deficiency is common in older individuals. This may be due to bleeding from the gastrointestinal or genitourinary tract, from cancer, peptic ulcer, nonsteroidal anti-inflammatory drug-induced gastritis, diverticular disease of the colon, or angiodysplasia. *Helicobacter pylori* gastritis may cause iron deficiency, as the bacterium utilizes food iron for its own growth. In some cases, the cause of iron deficiency is not found.[27] Some of these cases may be nutritional, as age-related gastric atrophy may prevent the reduction of food-bound iron necessary for its absorption. Cobalamin deficiency may be present in as many as 15% of individuals aged 60 and older.[28,29] Cobalamin deficiency is most commonly due to an inability to digest food-bound B12 because of gastric atrophy. Crystalline cobalamin is absorbed normally in this situation, and oral preparations of B12 may correct the deficiency. If folate deficiency is not present as well, cobalamin deficiency may not cause anemia but may cause peripheral neuropathy and dementia. Myelophthisis is more common in hematologic malignancies, but it 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 increased concentration of immature blood cells in the circulation.

Diagnostic Investigation for Anemia in the Older Person

In older individuals, anemia may be multifactorial, which may affect its clinical presentation. For example, iron deficiency tends to produce a microcytic anemia, whereas cobalamin deficiency leads to a macrocytic condition. A combination of the two deficiencies may lead to a normocytic anemia. It is prudent to explore all common causes of anemia in an older person presenting with hypoproliferative anemia, irrespective of the mean cellular volume. These possibilities include iron, cobalamin, and folate deficiency; hypothyroidism; and anemia of renal insufficiency. Iron deficiency presents with low serum iron, high iron-binding capacity, low ferritin levels, and high levels of soluble transferring receptor (sTf), whereas ACI presents with low serum iron, low iron-binding capacity, high ferritin, and low sTf levels. sTf is probably the most sensitive test with which to distinguish the two conditions. Cook et al have devised a way to estimate total body iron from the ratio of circulating sTf and ferritin. Cobalamin deficiency is definitely present for circulating levels < 150 pg/mL. A number of reports, however, have demonstrated that elevated levels of methylmalonic acid (MMA), reflecting cobalamin deficiency, may be present for levels of cobalamin as high as 350 pg/dL. Thus, when cobalamin levels are between 150 and 350 pg/dL, it may be reasonable to check MMA levels as well. Anemia of renal insufficiency may be suspected in all cases of normocytic anemia with low circulating levels of erythropoietin, when the creatinine clearance is lower than 60 mL/min.

Bone marrow aspiration with cytogenetics and fluoroctometry should be performed in all cases of pancytopenia (unless cobalamin deficiency has been conclusively demonstrated) and in all cases in which the cause of anemia is not clearly apparent, to rule out myelodysplasia or myelophthisis. If infection is suspected, bacterial and fungal cultures of the bone marrow should also be obtained. When to begin evaluating the older person for anemia remains unclear. Based on the evidence reviewed, it appears reasonable to consider as anemic values of hemoglobin lower than 13 g/dL in both men and women. If a cause of anemia is not found, it may be reasonable to consider values of hemoglobin between 12 and 13 g/dL to be normal for that particular individual, especially if the value remains constant for 1 year or longer. Levels of hemoglobin < 12 g/dL should always be considered abnormal, even if the cause of anemia is not immediately apparent. Another unanswered question is whether one should always perform a bone marrow examination in subjects with mild anemia (hemoglobin levels between 11 and 12 g/dL), when other causes of anemia are not immediately apparent. This examination would help the diagnosis of early forms of myelodysplasia, but it is not clear that early treatment of this condition would improve overall survival or delay progression to acute myeloid leukemia.

Complications of Anemia in the Older Person

Anemia has been associated with a number of unfavorable outcomes in the older person. These include the following possibilities:

- Increased mortality rate has been reported in at least six studies. Of these, the WHAS was particularly significant, as it demonstrated increased risk of mortality for hemoglobin levels below 13.4 g/dL, which in the past had been considered normal for both women and men.

- Reduced cognitive function and dementia. In dialysis patients, failure to correct anemia was associated with an increased risk of dementia. Likewise, the development of cognitive deficits in the course of adjuvant chemotherapy of breast cancer was more common in anemic patients.

One recent study found a direct association between anemia and reduced cognitive performance in individuals aged 65 and older and another concluded that anemia was a risk factor for dementia. Along the same lines, hemoglobin levels below 10 g/dL were associated with a threefold increase in postoperative delirium in patients 70 and older undergoing elective hip replacement.

- Increased risk of congestive heart failure and coronary death. Chronic anemia has been associated with left-ventricular hypertrophy and eventually congestive heart failure. Anemia was also an independent risk factor for death in patients admitted to a coronary care unit with unstable angina.

- Fatigue and functional dependence. Several studies in cancer patients of all ages have demonstrated that fatigue was the most common chronic symptom of cancer and was associated with an increased emotional and physical burden on the caregiver. Fatigue was inversely related with hemoglobin levels and was improved by the correction of anemia. In older individuals, anemia has been associated with decreased mobility, decreased performance of physical exercise, and
functional dependence.[6,36,44,45]

- In cancer patients, anemia may have other negative effects including enhanced risk of chemotherapy-induced toxicity,[46,47] reduced response to treatment,[48] and increased number of blood transfusions.[48] As the majority of chemotherapy agents are heavily bound to red blood cells, in the presence of anemia the concentration of free drugs—and consequently the risk of toxicity—may be increased.[47] The response of cervical and head and neck cancer to radiation therapy was reduced in patients with anemia.[49] Decreased tissue oxygenation apparently did prevent the formation of free radicals after exposure to radiation.

Blood transfusions may cause four types of complications: infections, transfusion reactions, transfusion refractoriness, and worsened cancer outcome. Although the risk of transfusion-related infections has been minimized, minor transfusion reactions still occur in 10% to 15% of transfusion episodes. Several studies have demonstrated that cancer patients who had received red blood cell transfusions experienced a poorer outcome than those who had not received transfusions.[49]

Clearly anemia has numerous deleterious effects on the function, health, and quality of life of older individuals. Patients whose anemia has a clear cause, such as iron or cobalamin deficiency, should receive proper treatment. The advent of commercial preparations of erythropoietic growth factors allows the opportunity to reverse anemia due to relative erythropoietin insufficiency (eg, ACI, which may account for many cases of idiopathic anemia in the elderly). This approach should be studied in randomized controlled studies, because the management of cancer-related anemia, one of the most common forms of ACI, suggests that there may be some long-term risk in the reversal of anemia with erythropoietic growth factors.

### What We Have Learned From the Management of Cancer-Related Anemia

#### Erythropoietic Growth Factors

Currently available preparations include epoetin alfa (Epogen, Procrit), epoetin beta (available only in Europe), and darbepoetin alfa (Aranesp).[1] Darbepoetin alfa differs from epoetin alfa by the insertion of glycosil residuals in the epoetin molecule with the goal of prolonging its half-life. Thus, darbepoetin maintains its efficacy when administered every 3 weeks.[1]

Other erythropoietic stimulators are undergoing clinical trials. Continuous erythropoietin receptor activator (CERA) is a molecule of epoetin with a polymeric side chain that prolongs its half-life to several weeks[50] and may require less frequent administration than darbepoetin. A completely synthetic erythropoietic stimulator, Hematide, has been prepared and is undergoing early clinical experimentation.[51]

### Management of Cancer-Related Anemia

The goals of managing anemia in cancer patients include reduction in the need for blood transfusions, improvement of fatigue and quality of life, improved therapeutic response to antineoplastic treatment, and improved survival. The first two goals—reduction in blood transfusions and improved energy and quality of life—have been obtained beyond doubt in randomized clinical trials and have been confirmed in a recent meta-analysis of these trials.[52] However, no proof has been provided of improved cancer outcome and more prolonged survival.

In fact, a disturbing trend has emerged from seven randomized clinical trials, two of which have been published.[1] The goal of these trials was to obtain and maintain normal hemoglobin levels during cancer treatment. In each of these studies, patients treated with erythropoietic growth factors experienced a shortened survival, perhaps due, in part, to an increased risk of thrombotic events.[53] The possibility that erythropoietic growth factors might have stimulated tumor growth is not supported, as the number of cancer-related deaths was similar in patients receiving growth factors and in controls.

Based on these results, it appears reasonable to try to maintain the hemoglobin levels of cancer patients at around 12 g/dL. No increased risk of death was reported for this level of hemoglobin, which is also associated with the best gain in energy.[18] This is also the recommendation found in guidelines from major organizations, including the National Comprehensive Cancer Network, American Society of Clinical Oncology, and American Society of Hematology.

### Conclusions

1. The prevalence and incidence of anemia increases with age.
2. Anemia has been associated with reduced survival, increased risk of heart failure, and functional and cognitive decline in the older person. In cancer patients, it has also increased the risk of therapeutic complications.
3. In 70% to 85% of cases, the cause of anemia has been identified; in the remainder, the cause is not immediately apparent. While some of these cases may represent unrecognized renal insufficiency and/or early myelodysplasia, others may result from age-related relative erythropoietin
insufficiency—a condition germane to ACI.

(4) When identified, the cause of anemia should be reversed. Patients with chronic renal insufficiency related to anemia benefit from erythropoietin treatment for hemoglobin levels lower than 12 g/dL. (5) In patients with cancer-related anemia, hemoglobin levels around 12 g/dL should be maintained with erythropoietic growth factors.

(6) While it is reasonable to hypothesize that erythropoietic growth factors are beneficial for all older patients with ACI, this practice needs to be validated in randomized clinical trials, given the potential risks associated with erythropoietic growth factors demonstrated in cancer patients.

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The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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