



Paul Gauguin. *Café in Arles*, 1888. Oil on canvas.

The effects of anemia on survival, function, quality of life, tolerance of treatment, and clinical outcomes are particular concerns for elderly patients with cancer.

Anemia, Cancer, and Aging

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Background: *Anemia is an issue of concern in the management of older patients with cancer. In this age group, the incidence and prevalence of both cancer and anemia increase with age.*

Methods: *The clinical consequences and the management of anemia, a common comorbid condition in older patients with cancer, are explored.*

Results: *Common causes of chronic anemia include iron deficiency and anemia of chronic disease. The prevalence of vitamin B₁₂ deficiency due to reduced absorption of food-bound vitamin B₁₂ also increases with aging. Although in many cases the cause of anemia is not found, a primary deficiency of erythropoietin may be at fault in at least some of these cases since the response of erythropoietin to anemia may decrease in individuals over age 70.*

Conclusions: *Anemia should not necessarily be ascribed to cancer or aging. The causes of anemia should be pursued and reversed, and hemoglobin levels should be maintained at a minimum of 12 g/dL in cancer patients undergoing chemotherapy who are responsive to erythropoietin. The reversal of anemia may offset or delay the accumulation of catabolic cytokines that may be responsible for functional decline in aging individuals.*

Introduction

The older population is undergoing a continuous expansion in the United States as a result of more prolonged life expectancy and reduced natality: in 1990, 30 million individuals were aged 65 years and over, and this age group is expected to comprise 80 million people by 2050.¹ Currently, 60% of all cancers occur in persons over 65 years of age, and cancer in older individuals is expected to become progressively more common, with 80% of all cancers occurring in this population by the year 2050.² One of the major issues in the man-

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agement of cancer in older individuals is the high prevalence of comorbidity that may affect the function, the functional reserve, the life expectancy, and the tolerance of treatment by older individuals.³ This article explores the clinical consequences and the management of anemia, one of the most common comorbid conditions in older cancer patients.⁴

Definition and Epidemiology of Anemia

The incidence and prevalence of anemia increase with age.⁵ The recognition of anemia is important for two reasons: (1) Anemia may represent the first sign of a serious underlying disease, such as cancer of the digestive system or vitamin B₁₂ deficiency, that may be lethal if left undiagnosed, and (2) anemia itself is associated with and may partly be the cause of a number of morbid conditions, including death, functional dependence, dementia, cardiac failure, and increased risk of therapeutic complications such as toxicity of cytotoxic chemotherapy.⁶⁻¹⁰

According to the World Health Organization (WHO), anemia is defined as a hemoglobin level of less than 13 g/dL in men and less than 12 g/dL in women.⁵ The basis of this definition is the average hemoglobin level of healthy individuals. A number of physiologic

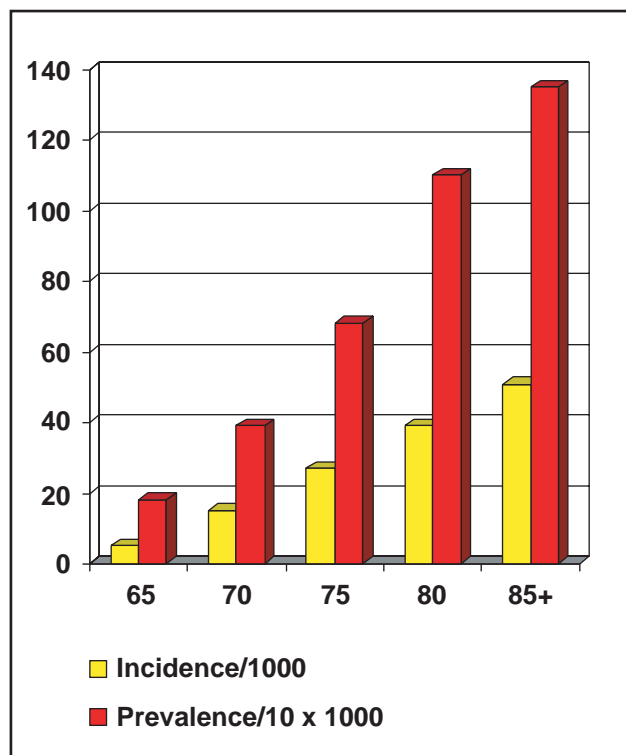


Fig 1. — Incidence and prevalence of anemia in Olmsted County (Minnesota) residents. Data from Ania BJ, Suman VJ, Fairbanks VF, et al. Prevalence of anemia in medical practice: community versus referral patients. *Mayo Clin Proc.* 1994;69:730-735.

findings support this definition. The secretion of erythropoietin is increased when hemoglobin levels fall below 12 g/dL, indicating that these levels of hemoglobin are necessary for optimal tissue oxygenation, thus showing that tissue oxygenation is optimal above these levels.^{11,12} In anemic cancer patients, the maximal incremental improvement in energy levels and quality of life is obtained when the hemoglobin levels increase from 11 g/dL to 12 g/dL.¹³⁻¹⁵ The risk of surgical complication increases inversely for hemoglobin levels below 12 g/dL.¹⁶⁻¹⁸ However, the definition provided by the WHO may be too restrictive, especially in light of recent reports. The Women's Health and Aging Study, a cohort study of community-dwelling women 65 years of age and older, revealed that hemoglobin levels below 13 g/dL are an independent risk factor for mortality¹⁹ and disability.²⁰ Additionally, prospective studies reported that anemic cancer patients treated with epoetin alfa showed further improvement in energy levels when hemoglobin levels rose above 12 g/dL.^{14,15,20-22}

The prevalence of anemia increases markedly after age 60.^{5,23-25} Cross-sectional and cohort studies of residents of Olmsted County, Minnesota, confirmed the relationship of anemia and advancing age. Both prevalence and incidence started increasing by age 65, with steeper increases after age 80 (Fig 1).^{5,24} Of interest, the prevalence of anemia was higher among women before age 65 and among men thereafter. A likely interpretation of these data is that women are more susceptible to anemia at a younger age due to menstrual blood loss and childbearing iron loss, while men have a higher prevalence of anemia-related morbidity at an older age.

The association of anemia and age is a concern for the management of cancer, since the highest prevalence of cancer is found among older individuals. Of special interest to this review are the effects of anemia on survival, function, quality of life, and tolerance of treatment. It is important to examine the cause and the clinical consequences of anemia in older individuals to establish the reversibility of this condition. The possibility that correction of anemia might delay or reverse to some extent aging itself is also discussed.

Etiology and Pathophysiology of Anemia in the Elderly

Contrary to a common impression, aging by itself is unlikely to lead to anemia.^{26,27} Cross-sectional and longitudinal studies of healthy older individuals have shown that the average hemoglobin levels remain stable between ages 60 and 98.^{25,28,29} Two contrasting epidemiologic findings — the hemoglobin levels remain stable throughout the age spectrum^{25,28,29} but the inci-

dence and prevalence of anemia increase with age^{5,23} — suggest that anemia in older individuals is due to the increased prevalence of comorbidity in this population.

An interesting possibility, congruent with our understanding of age, is that older individuals become more vulnerable to anemia when faced by hemopoietic stress.^{30,31} Aging is associated with a progressive reduction in the functional reserve of multiple organs and systems³⁰; this association enhances the susceptibility to insufficiency of failure of those systems in presence of stress. In the case of hemopoiesis, the hemopoietic reserve may become compromised by a number of factors including reduced concentration of hemopoietic stem cells, reduced sensitivity of stem cells and hemopoietic progenitors to growth factors, reduced production of growth factors, increased circulation of substances that inhibit hemopoiesis in the circulation and in the hemopoietic microenvironment, and compromised ability of the microenvironment to home and nurture these elements.³¹ These possibilities have been recently reviewed, as follows:

- The evidence that the number of pluripotent hemopoietic stem cells declines with age is inconclusive at best, in both experimental animals and humans. In any case, if the concentrations of these elements were to decline with age, they appear more than sufficient to maintain hemopoiesis during the human lifespan, even when faced with hemopoietic stress.³¹ It is possible, however, that their proliferative and self-replicative ability, as well as their plasticity (ie, the ability of the stem cell to engage into different hemopoietic lines), may be reduced, thus possibly compromising response to stress. These possibilities need to be assessed.

- Likewise, the production of hemopoietic growth factors does not appear to reduce with age. In a num-

ber of older individuals, the production of erythropoietin appeared to be inadequate to correct the level of anemia, but in at least some of these individuals, undiagnosed renal insufficiency might have been present.³¹

- The sensitivity of hemopoietic stem cells and progenitors to growth factors might be reduced. The increment of these elements in the circulation following granulocyte-macrophage colony-stimulating factor (GM-CSF) is lower in older men compared with their younger counterparts, though the increase in circulating granulocytes and erythrocytes in response to pharmacologic doses of filgrastim and erythropoietin is well maintained with age.³¹

- The best evidence suggests that aging is associated with circulating substances, namely, cytokines that may compromise the response of stem cells and hemopoietic progenitors to growth factors. This possibility is interwoven with the recent reports that increased concentrations of interleukin-6 (IL-6) is associated with increased risk of death and functional decline in older individuals.^{32,33} Increased IL-6 concentrations have also been associated with increased risk of anemia and geriatric syndromes.³⁴ Aplastic anemia, which occurs more commonly in advancing age, is an autoimmune disorder associated with inhibition in proliferation and maturation of hemopoietic stem cells.³⁵

In addition to these quantitative changes, it is important to remember that qualitative changes of hemopoiesis may also occur with age and compromise the hemopoietic reserve. To a large extent, myelodysplasia, which also occurs more often with age, is caused by the inability of hemopoietic progenitors to mature and differentiate.³⁶

Table 1 summarizes two reports on the common causes of anemia in the elderly. One report included the whole population of Olmsted County, Minnesota,²⁴ and the second report was based on discharges from a single hospital.³⁷ Of special interest in this review is the high prevalence of anemia of unknown cause, which also has been reported in other articles.³¹ This may reflect to some extent inadequate workup, early forms of myelodysplasias, and absolute or relative erythropoietin deficiency. The main cause of absolute erythropoietin deficiency is probably renal insufficiency, which occurs more frequently with age,^{30,38,39} while relative erythropoietin deficiency may be related in part to inhibition of erythropoiesis by circulating cytokines. The anemia of chronic disease is a good example of anemia where cytokines inhibit erythropoiesis by reducing the sensitivi-

Table 1. — Primary Causes of Anemia

Cause	Prevalence (%)	
	Joosten et al ³⁷ *	Anía et al ²⁴ **
Chronic disease	35	17
Unexplained causes	17	36
Iron deficiency	15	15
Posthemorrhagic	7	7
Renal failure, liver and endocrine disease	6.5	8
Myelodysplasia or acute leukemia	5.5	-
Chronic leukemia or lymphoma	5.5	-
Vitamin B ₁₂ or folate deficiency	5.5	-
Other hematologic disease	3	17

* hospital discharges
 ** residents of Olmsted County, Minnesota

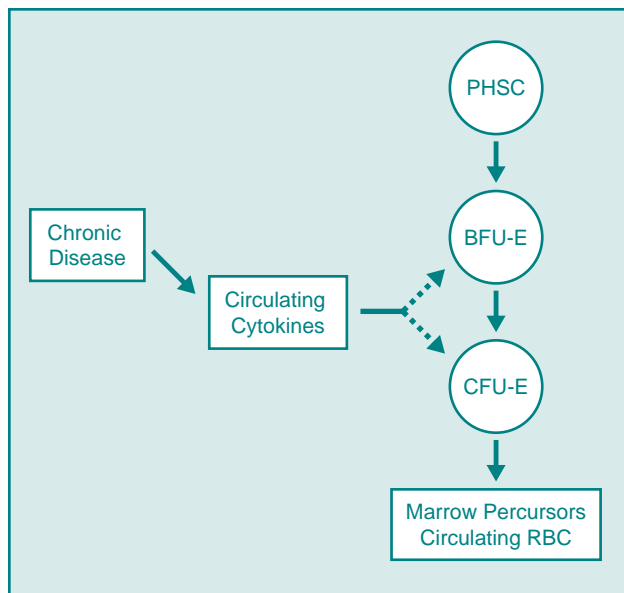


Fig 2. — Pathophysiology of anemia of chronic disease (PHSC = pluripotent hemopoietic stem cell, BFU-E = burst forming unit-erythroid: early erythropoietic progenitor, CFU-E = colony-forming unit-erythroid, late erythropoietic precursor, RBCs = red blood cells).

ty of erythropoietic progenitors to erythropoietin⁴⁰ (Fig 2). Anemia secondary to erythropoietin deficiency may be reversed with epoetin alfa and darbepoetin alfa.

Pathogenesis and Management of Anemia in Older Patients

Iron Deficiency Anemia

Iron deficiency is mainly due to chronic blood loss from ulcers, cancer, diverticula, or angiodysplasia.^{23,41-43} The role of reduced blood absorption is unclear but may be relevant in the oldest old and in elderly women whose recurrent blood loss during reproductive years (menstruations, pregnancies, and lactation) has not been adequately replaced. Regardless of sex, blood loss should be thoroughly investigated for the presence of iron deficiency; failure to do so may compromise the curability of some diseases such as cancer.

Iron deficiency is documented by low serum ferritin levels, high total iron-binding capacity (TIBC) and transferrin levels, low transferrin saturation, high concentration of free transferrin receptor, and absence of bone marrow iron stores.^{23,41-45} Microcytic, hypochromic anemia is a hallmark of iron deficiency, but even in the absence of this disorder in older individuals, iron deficiency should be suspected because multiple deficiency with opposite effects on red blood cell size may be present. Bone marrow examination is seldom necessary today. When the concentration of iron, iron-binding capacity, and transferrin are inconclusive,

determination of transferrin receptor is generally sufficient for the diagnosis.

Anemia of Chronic Disease

Anemia of chronic disease is probably the most common form of anemia in the elderly.^{24,37-40} The severity of the anemia generally correlates with the severity of the underlying disease.²⁴ It is important to note that in some cases, the chronic disease responsible for anemia cannot be identified.⁴⁰ Anemia then expresses a hemopoietic injury accumulated during the years.⁴⁰ This concept is germane to the current concept of aging, which is defined as the progressive decline in the functional reserve of multiple organs and systems caused by a number of injuries accumulated over time and expressed by an increase concentration of circulating cytokines³¹⁻³³ that at a certain point becomes self-maintained. An appealing consequence of this concept is the possibility that correction of anemia may stop or slow down the aging process and prevent aging-related functional decline.

Regardless of the original cause of anemia, patients with this condition cannot mobilize and utilize iron that is present in excess in the reticulo-endothelial cells of the marrow. Patients with anemia of chronic disease usually have low serum iron, low or normal TIBC, normal or high serum ferritin levels, and low concentrations of soluble transferrin receptor.^{23,44,45}

Two groups of anemia of chronic disease are recognized: *rheumatoid arthritis type* and *cancer type*. The rheumatoid arthritis type involves inhibition in the maturation of late hematopoietic stages and is more sensitive to erythropoietin⁴⁰ than the cancer type. This involves inhibition of a more primitive erythropoietic precursor and responds only to erythropoietin in high doses.^{12,13} Decreased red blood cell survival may also contribute to the pathogenesis of anemia of chronic diseases.⁴⁰ Other mechanisms involved in anemia of chronic disease may include inadequate production of erythropoietin that may be compounded by increased resistance to erythropoietin (Fig 2).^{40,45}

An important issue that is presently unresolved concerns the effect of catabolic cytokines on the production of erythropoietin. This effect is germane to the focus of this discussion since aging is associated with increased concentration of these cytokines³¹⁻³³ and in some older individuals, the production of erythropoietin in response to anemia is inadequate.⁴⁶⁻⁵⁰ Though age-related involution of the renal tissue may explain in part this relative erythropoietin insufficiency, it is appealing to connect the catabolic cytokines that are a hallmark of aging³² to decreases in both production of responsiveness to erythropoietin.

In any case, increased prevalence of comorbidity, increased concentration of catabolic cytokines, and reduced ability to produce erythropoietin seem to cause older individuals to be particularly susceptible to anemia of chronic disease. In turn, anemia may cause anoxia and may increase susceptibility to disease that may aggravate anemia and accelerate aging. It is a tantalizing concept that correction of anemia may break this vicious cycle.

Anemia of Renal Insufficiency

A progressive decline in glomerular filtration rate is the most common age-related physiologic change.³⁰ Thus, it would not be surprising if a number of older individuals experienced a reduction in their ability to produce erythropoietin and developed anemia of chronic renal insufficiency.⁴⁹ Reduced red blood cell survival may also occur and aggravate anemia.^{50,51} This type of anemia is normocytic and normochromic, and it may have long-term consequences including congestive heart failure, reduced cognition, and lethargy.⁴⁹ These manifestations may interfere with the patient's daily function, reduce survival, and compromise quality of life.⁴⁹ Fortunately, most of these complications can be prevented by managing anemia with epoetin alfa.^{49,50}

Anemia of Vitamin B₁₂ Deficiency

A deficiency in vitamin B₁₂ should be suspected in all elderly individuals with circulating levels of cobalamin within the lower limits of normal but equal to or lower than 300 pg/mL.⁵²⁻⁵⁴ Approximately 15% of these individuals present with an elevated circulating level of methyl malonic acid or histidine, which indicates vitamin B₁₂ deficiency.⁵³ Another sign of this deficiency is the fact that reticulocyte counts will increase following administration of vitamin B₁₂. A deficiency of vitamin B₁₂ in the elderly is seldom caused by pernicious anemia; in most cases, the deficiency results from decreased digestion of food-bound vitamin B₁₂ due to increased gastric pH and reduced pepsin production.⁵²⁻⁵⁴ It is important to note that a deficiency in vitamin B₁₂ may be present in the absence of anemia when folate levels are normal or elevated. In this case, the main manifestations of vitamin B₁₂ deficiency are neurological, including peripheral neuropathy, posterior column dysfunction, and reduced cognition.⁵⁴ Given the high risk of vitamin B₁₂ deficiency in the aged and the risks of this condition, some authors have proposed that all individuals 60 years of age and older be screened periodically for this deficiency.⁵²⁻⁵⁴

When anemia is present, it is generally hyporegenerative, macrocytic, and associated with some degree of pancytopenia.⁵²

Anemia of Unknown Causes

In 17% to 32% of cases, the cause of anemia is unknown.^{5,37} These cases likely represent a wide array of situations including inadequate diagnostic investigations, early cases of myelodysplasia, and unrecognized renal insufficiency. Some of these cases may represent an early exhaustion of erythropoietic progenitors and inadequate erythropoietin production. Studies examining the relationship between hemoglobin and erythropoietin levels in older and younger individuals have produced conflicting results. Goodnough et al⁵⁵ and Powers et al⁵⁶ found either no apparent differences in the production of erythropoietin in anemic individuals aged 65 and over compared with their younger counterparts or only a slight increase in production observed in the erythropoietin response in the elderly (≥ 65 years) compared with younger (< 65 years) patients. However, other authors showed that the production of erythropoietin in response to anemia was compromised in individuals over age 70 (in other studies, a statistically significant lower erythropoietin response to anemia was demonstrated in patients ≥ 70 years of age compared with those < 70 years of age.⁴⁶⁻⁴⁸ It appears reasonable to assume that inadequate production of erythropoietin may be a cause of anemia among some older individuals and to recommend that erythropoietin levels be checked as part of the anemia workup.

Proposed Diagnostic Workup for Anemia in the Elderly

In the older population, the diagnosis of anemia may be delayed by a number of age-related conditions such as decreased perception of symptoms or to the erroneous attribution of fatigue to old age or to preexisting conditions.⁵⁷ Ongoing studies are exploring the advisability of screening older individuals for anemia. Failure to diagnose is rarely a consideration in patients with a diagnosis of cancer since virtually all of these patients undergo a complete blood count test as part of their general assessment. Still, it is important to avoid the assumption that anemia is necessarily due to cancer or age in these individuals. Given the high presence of comorbidity among the elderly, anemia may have other causes that are unrelated to cancer and are correctable. One such cause may be another malignancy, given the increased prevalence of multiple primary malignancy in the aged.⁵⁸

Specific laboratory tests to ascertain the causes of hyporegenerative (low reticulocyte count) anemia and the possible its treatment strategies for this most common anemia are listed in Table 2. In the absence of inflammation, serum ferritin levels faithfully mirror the total body iron stores.⁵⁹ Serum ferritin levels of less

Table 2. — Recommendations Concerning Laboratory Tests for Diagnostic Workup of Hyporegenerative Anemia (Low Reticulocyte Count)

Laboratory Test	Type of Anemia
Reticulocyte count	All cases
Iron, transferrin, ferritin	Microcytic and normocytic anemia Hyporegenerative anemia
Vitamin B ₁₂ , folate	Macrocytic and normocytic anemia Hyporegenerative anemia
Erythropoietin levels	All cases of hyporegenerative anemias
Serum creatinine	All patients
Cytogenetics	Suspicion of myelodysplasia or other neoplastic diseases

than 15 ng/mL indicate that iron deficiency is likely and that martial treatment should be initiated.^{23,59} Anemia of chronic disease should be suspected when patients display low serum iron, low or normal TIBC, normal or high serum ferritin levels, and low soluble transferrin receptors. In cancer patients as well as in patients with rheumatoid arthritis, treatment with erythropoietin is effective in the majority of patients and should be considered.^{12-16,21,22} Measurements of erythropoietin levels and glomerular filtration rates should be performed in all anemic patients because relative erythropoietin insufficiency may contribute to the pathogenesis of this condition. In addition, bone marrow examinations should be performed in all cases of pancytopenia (except those due to vitamin B₁₂ deficiency), suspected myelophthisis (including infection of the bone marrow), and cancer or fibrosis, and also whenever the cause of anemia is not evident from less invasive studies. During each bone marrow examination, cytogenetic tests and flow cytometry should be performed to investigate the diagnosis of myelodysplasia, and iron stains should be obtained to identify the iron concentration.

Clinical Implications of Anemia

Common clinical complications of anemia are listed in Table 3.

Anemia and Survival

At least five studies have shown that anemia is associated with a decreased survival rate in older individuals. The 5-year mortality rate of individuals aged 85 and over increased almost twofold in the presence of anemia, and anemia was as an independent risk factor for death in a Dutch study.⁶⁰ The risk of mortality increased with the degree of anemia. Almost identical results were reported by Kikuchi et al⁶¹ among elderly Japanese and

Table 3. — Clinical Implications of Anemia

Reduced survival
Reduced function and quality of life
Increased risk of congestive heart failure
Increased risk of myocardial infarction
Increased risk of dementia
Increased risk of pharmacological complications

by Ania et al⁵ among residents in Olmsted County, Minnesota. In a retrospective study by Gagnon et al,⁶² anemia was associated with increased risk of cardiovascular death in persons over age 70. Particularly provocative is the study of Chaves et al¹⁹ that showed hemoglobin levels lower than 13.4 g/dL to be an independent risk factor for mortality among home-dwelling women aged 65 and older. These authors also found that the risk of dying decreased 0.76 times for every increase of 1 g/dL in hemoglobin between 8 and 9 g/dL.

Anemia, Fatigue, and Functional Dependence

Fatigue is the most common and vexing chronic symptom of cancer and cancer treatment.⁶³ Fatigue is particularly common after 65 years of age⁶⁴ and may lead to progressive functional decline, delayed cancer treatment, suboptimal cancer control, and substantial increases in the costs of managing these patients.⁶⁵

The causes of fatigue include energy imbalance and emotional distress.⁶⁶ Anemia is the most common cause of energy imbalance, as demonstrated by the fact that correction of anemia in older cancer patients resulted in improved energy levels^{12-15,21,22} and also that this effect was partly independent from response of cancer to chemotherapy.¹⁵ Of special interest, the level of energy in cancer patients treated with erythropoietin increased with the level of hemoglobin up to and beyond values of 12 g/dL.¹⁴ These findings suggest that correction of anemia in older individuals may improve the tolerance of and response to treatment and may even prolong survival. Most important, prevention of fatigue may reduce the risk of functional dependence, which is expensive.

Anemia and Cardiovascular Complications

Chronic anemia may lead to left ventricular hypertrophy due to chronically increased cardiac output.⁶⁷ Every decrease in hemoglobin of 1 g/dL is associated with an increase in the risk of left ventricular hypertrophy by 6%.⁶⁷ Prior to the advent of erythropoietin, which allowed correction of anemia in virtually all renal patients, congestive heart failure was a common complication of renal failure.⁶⁸

In older individuals, anemia is an adverse risk factor both for congestive heart failure and for death from coronary artery disease. Silverberg et al⁶⁹ found that the severity of anemia highly correlated with congestive heart failure in persons aged 70 and over. They also reported that in this age group, the incidence and severity of congestive heart failure significantly correlated with circulating hemoglobin levels. In the presence of severe anemia (ie, hemoglobin <5 g/dL), congestive failure developed even in the absence of preexisting cardiovascular disease. Wu and colleagues⁷⁰ reported that the mortality from coronary artery disease in a coronary care unit increased for patients aged 65 and older if the hematocrit was below 33% and they did not receive blood transfusions.

Anemia and Cognition

A correlation between anemia and risk of Alzheimer disease was first identified by Beard et al.⁷¹ A number of cognitive and emotional complications of anemia, including headaches, loss of concentration, and depression, have been reported in cancer patients.⁷²⁻⁷⁴ In patients undergoing dialysis, anemia was associated with confusion, inability to concentrate, decreased mental alertness, and impaired memory.⁷⁵ A direct correlation between hemoglobin levels and cognition was established by Pickett et al,⁷⁶ and they reported that increasing the hematocrit of chronic dialysis patients above 33% to 36% with blood transfusions improved attention span, learning ability, and memory.

Anemia and Iatrogenic Complications

Anemia may increase the risk of adverse drug reactions by reducing the percentage of drugs bound to red blood cells and increasing the concentration of free drug in the circulation and also by causing tissue hypoxia that increases the susceptibility of these tissues to therapeutic complications.^{6-10,77} Common antineoplastic drugs bound to red blood cells include anthracyclines, alkaloids, and camptothecins. In postoperative hospitalized patients over 70 years of age, anemia was associated with an increased risk of delirium.⁷⁷

At least five studies showed that the risk of complications of cytotoxic chemotherapy, especially myelosuppression, increases in the presence of anemia.⁶⁻¹⁰ In younger individuals, the effects of anemia may be buffered in part by other tissue; this compensatory mechanism may be missing in older patients due to sarcopenia.^{78,79} Anemia appears to be associated with a general condition of poor health that may compromise the outcome and quality of life of older patients with cancer. Management of anemia should be a priority in these patients.

Conclusions

The prevalence of both cancer and anemia increases with age. In addition to heralding an underlying disease, anemia is by itself a cause of mortality, functional decline, cardiovascular and central nervous comorbidity, and increased risk of therapeutic complications. Anemia may adversely influence the management of older cancer patients receiving chemotherapy and radiotherapy by limiting the dose, the dose intensity, and the dose density of the treatment and thus preventing adequate cancer control. In addition, anemia may increase the cost of treating cancer by causing prolonged disability and more frequent hospitalizations.

The causes of anemia in older cancer patients should be thoroughly pursued and corrected. In the majority of cases, a relative erythropoietin deficiency may be present, which is reversible with erythropoietin.

The assumption that anemia is automatically ascribed to cancer or age could lead to overlooking treatable comorbid conditions, delaying their management, diminishing their curability, and compromising the management of cancer.

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