Anemia of Aging: A Model of Erythropoiesis in Cancer Patients

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Anemia produces deleterious effects in the older patient with cancer and corresponds with an increasing prevalence of comorbid conditions. Erythropoietin can improve anemia of chronic disease, the most common form of anemia in the elderly.

Introduction

The adverse effects of anemia in cancer patients include fatigue and enhanced chemotherapy-related toxicity. Anemia is particularly threatening for the older person with cancer who can have multiple comorbid conditions that may either cause anemia or aggravate the effects of anemia on other tissues. Because the functional reserve of different organ systems becomes progressively restricted with age, the older individual may also be susceptible to the complications of anemia.

In this review, we explore the hematopoietic changes of aging and the prevalence, incidence, and causes of anemia in the older person. The effective management of anemia in these individuals is also discussed.

Hemopoiesis and Aging

A common view of hemopoiesis holds that a pluripotent hematopoietic stem cell (PHSC) gives origin to committed progenitors of myeloid, erythroid, and megakaryocytic lineages, and these, in turn, give origin to the recognizable hematopoietic precursors of the bone marrow (Figure). This process is modulated by a number of growth factors and by the hematopoietic microenvironment. In the case of erythropoiesis, one may distinguish an early progenitor, burst-forming unit-erythroid (BFU-E), and a late progenitor, colony-forming unit-erythroid (CFU-E). The proliferation of the BFU-E is stimulated by burst-promoting activity (BPA) and, to a lesser extent, by erythropoietin. The relative insensitivity of BFU-E to erythropoietin is due to low concentration of erythropoietin receptors. The proliferation of CFU-E is mainly stimulated by erythropoietin.

Anemia of Aging: Factors to be considered in this anemia of aging. SCGF = stem-cell growth factor. EPO = erythropoietin.

Aging may favor the development of anemia due to a reduction in PHSC reserve, reduced production of growth factors, reduced sensitivity of stem cells and progenitors to growth factors, and microenvironmental abnormalities. In experimental systems, Lipschitz et al studied the concentration of hemapoietic stem cells in younger and older animals during baseline conditions and hematopoietic stress. The concentration of PHSC at baseline was similar in mice of different ages, but it declined in the older animals during hematopoietic stress. These results suggest an age-related restriction of stem-cell reserve. In humans, several observations suggest a progressive exhaustion of PHSC. The hematopoietic tissue of the marrow contracts progressively with aging. The age-adjusted cellularity of the bone marrow is represented by the equation 100 – age. Chatta et al compared the concentration of PHSC in the peripheral blood of persons older than age 70 and persons younger than age 30. They found that the baseline concentration of PHSC was similar for subjects of different ages, but following administration of growth factor (GM-CSF), younger individuals experienced a greater rise in the concentration of these elements. Hyrota et al compared the concentration of BFU-E in the bone marrow of younger and older individuals and found a decrement of these elements in the aged. However, this decrement was not associated with clinical anemia.

The production of erythropoietic growth factors in the elderly has been explored. A group of Italian investigators found that the production of BPA is reduced in the bone marrow of older individuals. The reduction appeared to be related to the declining concentration of helper T cells. In addition, the response of BPA to cimetidine was blunted in older individuals, suggesting an underlying dysfunction of suppressor T cells as well. Normally, cimetidine stimulates the release of BPA by reversing the inhibitory activity of suppressor B cells on erythropoiesis. The reduction in BPA did not correlate with clinical anemia, indicating that although physiologic changes of aging generally do not cause anemia, they may increase the older individual’s susceptibility to intervening causes of anemia.

Studies of erythropoietin production in older individuals are inconclusive. Joosten et al measured the serum erythropoietin concentration in patients aged 70 to 96 years with either iron-deficient anemia or anemia of chronic disorders. The levels were lower in patients with anemia of chronic disorders, and the authors concluded that the erythropoietin response may become blunted with age in persons with chronic anemia. Nafziger et al reported a lower concentration of erythropoietin in the serum of patients aged 70 to 95 years with iron-deficient anemia compared with younger anemic patients. This observation also suggested an age-related blunting of erythropoietin response. A study by Matsuo et al provided different results. These authors found similar serum erythropoietin concentration in anemic Japanese patients older than age 70 and younger than age 60. The reticulocyte count was lower in the aged, suggesting decreased sensitivity to erythropoietin. Kario et al compared the concentration of erythropoietin in the serum of younger and older individuals with iron deficiency and found that patients of both age groups experienced the same increment in erythropoietin production. The circulating levels of erythropoietin increased earlier in older individuals compared with their younger counterparts, that is before the hemoglobin concentration dropped below 12 g/dL. This observation suggests that hypoxia may be present at higher levels of hemoglobin in the elderly compared with younger individuals.

Tasaki et al studied a population of patients who donated their own blood for the purpose of autologous transfusions. They found that patients aged 65 years and older occasionally failed to mount an adequate erythropoietin response to blood loss. This suggests that erythropoietin production is generally not decreased in the aged. Some elderly persons, however, may show a compromised response to acute and chronic anemia. This compromise may result from concomitant diseases or...
from age-related exhaustion of erythropoietin-secreting ability. Goodnough et al.\textsuperscript{17} examined the effects of different doses of erythropoietin in autologous blood donors of different ages and found that the erythropoietic response was dose-dependent but age- and sex-independent.

Two studies have addressed the possibility that aging may be associated with declining sensitivity to erythropoietin. Cascino et al.\textsuperscript{18} found that patients over age 70 and younger patients with cisplatin-induced anemia experienced the same rise in hemoglobin concentration and the same decline in transfusion requirements when treated with equivalent doses of erythropoietin over the same period of time. Glaspy et al.\textsuperscript{1} treated 2,342 cancer patients aged 45 to 75 years with recombinant erythropoietin and found the erythropoietic dose to be independent of an age factor. Thus, aging may be associated with a progressive decline of PHSC that does not appear to cause anemia in the absence of stress. The production of erythropoietin and the sensitivity of erythropoietic precursors to erythropoietin do not appear to be affected by age. The effects of age on other aspects of erythropoiesis are poorly understood.

**Epidemiology and Pathogenesis**

The epidemiology of anemia in the elderly has been examined in three types of studies. Baldwin\textsuperscript{19} reviewed a number of longitudinal studies of aging populations and showed that, in the absence of new diseases, the hemoglobin concentration remained stable in most individuals, even after age 85. Inelmen et al.\textsuperscript{20} published a cross-sectional study from Italy of 1,784 healthy persons aged 65 and older and living at home. They found that the mean hemoglobin levels of this population remained almost constant throughout the oldest ages (Table 1). Ania et al.\textsuperscript{21} examined subjects in Olmsted County, Minn, and found that both increased with the age of the population (Table 2). Anemia was defined according to the criteria of the World Health Organization: hemoglobin concentration <13 g/dL in men and <12 g/dL in women.\textsuperscript{22} The authors identified the causes of anemia in 516 of 618 incident cases. The most common causes included acute blood loss from surgery or trauma, iron deficiency, chronic disorders, tumors, and nutritional or metabolic disorders. In 102 cases (16%), the causes of anemia remained unknown.

### Table 1. Mean Hemoglobin Concentration Among Healthy Individuals of Different Ages in Italy

<table>
<thead>
<tr>
<th>Age</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-69</td>
<td>13.77 ± 1.15</td>
<td>14.85 ± 1.33</td>
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<tr>
<td>70-74</td>
<td>13.75 ± 1.27</td>
<td>14.82 ± 1.40</td>
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<tr>
<td>75-79</td>
<td>13.44 ± 1.39</td>
<td>14.77 ± 1.43</td>
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<tr>
<td>80-84</td>
<td>13.44 ± 1.52</td>
<td>14.59 ± 1.47</td>
</tr>
<tr>
<td>≥85</td>
<td>13.34 ± 1.61</td>
<td>13.83 ± 1.13</td>
</tr>
</tbody>
</table>

### Table 2. Age-Related Prevalence and Incidence of Anemia in Olmsted County, Minn\textsuperscript{21,22}

<table>
<thead>
<tr>
<th>Age</th>
<th>Prevalence*</th>
<th>Incidence**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>65-69</td>
<td>18</td>
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<td>31</td>
</tr>
<tr>
<td>≥85</td>
<td>44</td>
<td>32</td>
</tr>
</tbody>
</table>

*per 100 persons
**per 100 persons/years

Similar observations were reported by Kirkeby et al.\textsuperscript{23} in Norway. Of 530 patients over 70 years of age seen in a general practice setting over an eight-month period, 72 were anemic; in 10 (14%) of these patients, the cause of anemia could not be identified. Likewise, Nilsson-Ehle et al.\textsuperscript{24} studied representative Swedish population samples aged 70, 75, and 81 years. They found that the prevalence of anemia and of anemia of unknown causes increased with the age of the population. The cause of anemia was identified in only 66% of 54 anemic patients aged 75 years and over by Sahadevan et al.\textsuperscript{25} in Singapore.

Inadequate workup or inadequate understanding of the causes of anemia at the time these studies were performed may account in part for the anemia of unknown origin in elderly individuals. For example, Carmel\textsuperscript{26} reported that 2% of 729 persons over 60 years of age in the Los Angeles area had undiagnosed pernicious anemia. Anttila et al.\textsuperscript{27} reported that approximately one third of elderly individuals with unexplained macrocytosis may eventually develop myelodysplasia. Some of these patients may be identified with special cytogenetic and molecular alterations.

Another explanation, decreased erythropoietin production, deserves consideration. At least three studies\textsuperscript{16,28,29} reported that a number of elderly patients with unexplained normocytic anemia had inappropriately low concentrations of erythropoietin in the serum. This observation suggests that aging may be associated in some patients with an inability to maintain an appropriate erythropoietin response to chronic anemia. This phenomenon was particularly evident in anemia of chronic disorders, including cancer. Thus, older individuals with cancer may be particularly prone to relative erythropoietin deficiency and may benefit most from treatment with erythropoietin.

**Diagnosis and Treatment**

Knowledge of certain diagnostic peculiarities of anemia in older individuals may help the practitioner to obtain a timely diagnosis of common and uncommon anemia. These are examined below.

**Cobalamin Deficiency**: The prevalence of cobalamin deficiency in community-dwelling persons 65 years of age and older may be as high as 5% to 15%.\textsuperscript{30,31} In many cases, anemia and macrocytosis are mild or even absent. The only clinical manifestations of B12 deficiency may include peripheral neuropathy and mild cognitive deficits, such as forgetfulness.\textsuperscript{32} The diagnosis should be suspected for values of serum B12 <30,\textsuperscript{31} The diagnosis may be confirmed in the research laboratory by elevated levels of methylmalonic acid, total homocysteine\textsuperscript{24} or by depletion of serum holotranscobalamin II\textsuperscript{33}; in clinical practice, the diagnosis may be confirmed by regression of clinical abnormalities after parenteral administration of cobalamin. The pathogenesis of cobalamin deficiency involves an age-related decrease in the absorption of protein-bound cobalamin in more than 50% of cases.\textsuperscript{34}
Iron Deficiency: Serum ferritin levels are useful for the diagnosis of iron deficiency. In persons over 65 years of age, ferritin levels of 35,36 By using these criteria, a diagnosis of iron deficiency may be obtained in approximately 75% of elderly patients without performance of bone marrow aspiration and biopsy.36

Unexplained Macrocytosis: The prevalence of unexplained macrocytosis increases after 75 years of age.37 After assessing serum B12 and folate levels, thyroid-stimulating hormone, and bone marrow examination, Mahmoud et al37 found the cause of unexplained macrocytosis in 75 (60%) of 124 elderly patients. The majority of the other cases had changes suggestive of early myelodysplasia. Anttila et al27 demonstrated the presence of cytogenetic and molecular abnormalities in approximately one third of 36 elderly patients with unexplained macrocytosis, thereby supporting the possibility of early myelodysplasia.

Anemia of Primary Autonomic Failure: This unusual form of anemia, which is associated with primary autonomic failure, was reported in 32 patients aged 65 years and older with primary autonomic failure.38 The pathogenesis of this anemia is unknown. In five patients, treatment with low doses of erythropoietin was attempted, and erythropoietin normalized the serum hemoglobin levels in all cases.

Anemia of Chronic Disorders: The pathogenesis of anemia of chronic disorders has been recently clarified.39 Many chronic disorders are associated with the production of cytokines that inhibit erythropoiesis. Interleukin 1 and interferon gamma are produced in excess in patients with cancer and chronic infections. These cytokines inhibit the proliferation of both BFU-E and CFU-E and cause a form of anemia responsive to high doses of erythropoietin (100 to 150 U/kg). Excess production of tumor necrosis factor (TNF) was reported in patients with cancer and rheumatoid arthritis. TNF inhibits the proliferation of CFU-E and induces an anemia sensitive to low doses of erythropoietin (50 U/kg).

Treatment

The treatment of anemia is the treatment of underlying causes. Anemia of chronic disorders is the main form of anemia in the aged, and this form of anemia responds best to erythropoietin.39 Treatment should be initiated at low doses (50 U/kg) three times a week; if adequate response is not seen within eight weeks, the dosage should be increased up to a maximum of 150 U/kg. Controversy exists concerning the timing of treatment. In view of the report from Cell’a40 that the optimal level of energy corresponds to a hemoglobin level of 11.5 to 12 g/dL, it is reasonable to institute treatment when the hemoglobin concentration drops below these levels.

Prophylactic treatment with erythropoietin should be considered for elderly cancer patients receiving chemotherapy.40 This approach appears particularly sensible in elderly patients who may not be able to maintain adequate production of endogenous erythropoietin in the presence of chronic anemia.15,28,29 An additional benefit to preventing anemia in older cancer patients is the prevention of chemotherapy-related toxicity that may be related to the reduction of red blood cell concentration. A reduction in red blood cell count may result in decreased red cell binding of some drugs (eg, mitoxantrone) and high free-drug concentration.41

Another situation in which the treatment with erythropoietin appears indicated is normocytic anemia of unexplained causes in elderly patients; this condition may be associated with a deficit of endogenous erythropoietin as well as the unusual anemia of primary autonomic failure.

Conclusions

Aging may be associated with a decreased reserve of PHSC and decreased ability to maintain the production of erythropoietin. These changes do not appear to cause anemia in the absence of stress. The prevalence and incidence of anemia that increase with age are largely related to the increasing prevalence of comorbid conditions. In 10% to 15% of cases, the cause of anemia may not be identified, and the serum erythropoietin levels are lower than expected.

Anemia of chronic disease is the most common form of anemia in the aged. The mainstay treatment of this anemia is erythropoietin. It is reasonable to institute treatment for patients with hemoglobin levels of less than or equal to 11.5 g/dL. Prophylactic administration of erythropoietin should be considered for older patients with cancer who are undergoing chemotherapy.

References


DR BENNETT

If you differentiate red cell production from granulocyte production or platelet production, the likelihood of seeing anemia is much greater as one ages because of comorbidity problems. But what has not been addressed much in the literature is change in the population of the lymphoid cells. I think there is evidence that as one ages, particularly over age 75 to 80 years, both B and T cells -- particularly T-cell subsets -- decrease. This may increase the likelihood of infection as well as the risk of secondary anemia occurring as a result.

DR BALDUCCI

The decline in T-cells may also, by itself, influence the cause of anemia. I don’t know exactly how much the T-cells are responsible for stimulating the hematopoietic stem cell, but there may be an interaction. However, it is not clear that immune senescence by itself, at least up to age 85, makes you more susceptible to disease. Certainly, if you have an infection and if your functional reserve becomes stressed, a problem may occur.