Anemia in Men With Advanced Prostate Cancer: Incidence, Etiology, and Treatment

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Anemia associated with advanced prostate cancer is a common occurrence. This article reviews the incidence and examines the various causes of this condition, including androgen deprivation, nutritional decline, bone marrow infiltration, treatment-related toxicity, and the chronic inflammatory state. Treatment of anemia in men with advanced prostate cancer is also discussed. In patients with limited bone marrow reserve, blood transfusions may be the only effective treatment.
[Rev Urol. *2004;6(1):1-4*]

Key words: Anemia • Prostate cancer • Androgen deprivation • Erythropoietin

Despite increased public awareness and widespread use of prostate-specific antigen (PSA) screening, adenocarcinoma of the prostate continues to be a major cause of morbidity and mortality for American men. In particular, anemia in patients with advanced prostate cancer causes significant morbidity. Symptoms caused by anemia, such as fatigue, malaise, lethargy, dyspnea, and tachycardia, are prevalent in this population and impede daily activities.[1]

Incidence

Although anemia associated with advanced prostate cancer is a common occurrence, the actual incidence of this condition can only be inferred from limited data. In a group of patients who underwent bilateral orchiectomy for prostate carcinoma, 78% experienced a mild anemia, with a decrease in hemoglobin level of 1 g/dL from baseline, and 29% demonstrated a decline of 2 g/dL or more.[2] In a study by Strum and colleagues,[3] of 133 patients undergoing total androgen blockade, 13% experienced a decline in hemoglobin level of 25% or more. In a similar study by Asbell and colleagues,[4] 2 months of combined androgen blockade led to anemia in 75% of patients, compared with fewer than 5% of patients who received goserelin acetate alone. Furthermore, approximately 30% of prostate cancer patients with metastases to the bone have anemia at the time of diagnosis.[5,6]

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Etiology

Anemia in men with advanced prostate cancer may be caused by several factors, including androgen deprivation, nutritional decline, bone marrow infiltration, treatment-related toxicity, and the chronic inflammatory state (Table 1). Castration is a well-documented cause of anemia, as testosterone is required for the enhancement of erythropoietin formation in the kidney, as well as for the marrow action of erythropoiesis. It has been demonstrated that, after castration, red blood cell mass decreases 10%, red blood cell diameter decreases 40%, and osmotic fragility increases.[7]

Fonseca and colleagues[2] have demonstrated a significant decline in hemoglobin level after orchiectomy alone. Combined androgen blockade, however, has been shown to cause a more substantial decline in erythropoiesis. In a study of patients undergoing orchiectomy for metastatic prostate cancer, the incidence of anemia was significantly higher in those who received flutamide than in those who underwent orchiectomy alone ($P = .024$).[8] Studies have also demonstrated a steep decline in hemoglobin level with total androgen blockade, a common therapy for advanced prostate cancer.[2,3]

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Replacement of normal marrow with cancer cells also contributes to anemia in men with prostate cancer. Anemia caused by bone marrow infiltration, called leukoerythroblastic anemia, is well described in various solid malignancies and causes an impaired hematopoiesis, which is evident on the peripheral blood smear. In a study by Shamdas and colleagues,[6] 28.6% of men with metastatic prostate cancer were found to have leukoerythroblastic anemia.

Other factors that may directly affect the bone marrow include previous or concurrent therapies, such as local radiation to bone marrow, systemic use of radiopharmaceuticals (strontium-89), systemic chemotherapy, and long-term use of combined androgen blockade.[2,9] The production of inflammatory cytokines by prostate cancer may also cause a decrease in erythropoietin production, leading to the anemia of chronic disease.[10] This myelosuppressive effect on red blood cell supply is believed to be mediated by moieties such as integrins, collagens, laminin, and other bone-derived proteins.

Hematuria and other sources of slow blood loss can also contribute to anemia in men with advanced prostate cancer. Typically, hematuria is caused by internal growth of the prostate into the urethra or growth of metastatic deposits within the wall of the bladder. Although rarely an acute threat to life, hematuria can cause much stress and frustration for both patients and caregivers. Attempts to manage hematuria in this setting include 3-way Foley catheter irrigation with the installation of agents such as alum, silver nitrate, and formalin. Cystoscopy may be beneficial to visualize and fulgurate the source of bleeding.

Table 1
Etiology of Anemia in Men With Advanced Prostate Cancer

- Androgen deprivation
- Marrow replacement
- Radiation therapy
- Radiopharmaceuticals
- Chemotherapeutics
- Anemia of chronic disease
- Inflammatory cytokines
- Hematuria
- Poor nutrition

Treatment

Although the role of continued hormonal therapy in patients with advanced prostate cancer has been a topic of debate following the results of a retrospective analysis by the Southwest Oncology Group,[11] a slight improvement in survival for patients who remained on hormonal therapy was demonstrated in a recent analysis by the Eastern Cooperative Oncology Group.[12] However, the possibility of a survival advantage must be weighed against the added threat of the normochromic, normocytic anemia that inevitably results from continued hormonal therapy. For patients with advanced prostate cancer, use of a luteinizing hormone-releasing hormone agonist without a peripheral androgen blocker may be beneficial in limiting anemia caused by complete androgen blockade.[1]

Because the development of anemia in patients with advanced prostate cancer is gradual, supportive measures can be attempted before transfusions become necessary. For patients who have not been deemed transfusion-dependent, the use of entities such as erythropoietin, iron preparations, and vitamin supplementation may be beneficial, although convincing randomized, prospective studies on this topic are lacking.

Given the effect of androgen deprivation and inflammatory cytokines on endogenous erythropoietin production, recombinant erythropoietin has been studied as a treatment option for men with anemia associated with prostate cancer. In a pilot study of 9 men with androgen-independent prostate cancer and anemia, recombinant human erythropoietin therapy, at a median dose of 150 U/kg administered subcutaneously 3 times a week, increased hemoglobin concentration by more than 10% in 7 men (78%).[13] Johansson and colleagues[14] also described a benefit with the use of recombinant erythropoietin: namely, a decrease in transfusion requirements and an improvement in quality of life.

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Low doses of dexamethasone are also being evaluated for the treatment of anemia related to advanced prostate cancer. An increase in hemoglobin was noted in 65% of patients receiving 0.5 mg to 2.0 mg of dexamethasone daily.[15]

Although supportive measures may offer benefit in some cases, many patients will have limited bone marrow reserve. For these men, blood transfusions are the only effective treatment and can help improve quality of life.

In summary, anemia in men with advanced prostate cancer is a complex, multifactorial process that may not be responsive to conservative measures. Blood transfusions may be the only effective therapy for some patients and should be considered early for symptomatic anemia. ■

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Main Points

- Anemia in men with advanced prostate cancer may be caused by several factors, including androgen deprivation, nutritional decline, bone marrow infiltration, treatment-related toxicity, and the chronic inflammatory state.
- Castration is a well-documented cause of anemia. Combined androgen blockade, however, has been shown to cause a more substantial decline in erythropoiesis.
- Replacement of normal marrow with cancer cells contributes to anemia in men with prostate cancer. Anemia caused by bone marrow infiltration, called leukoerythroblastic anemia, is well described in various solid malignancies and causes an impaired hematopoiesis.
- Hematuria and other sources of slow blood loss can also contribute to anemia in men with advanced prostate cancer. Typically, hematuria is caused by internal growth of the prostate into the urethra or growth of metastatic deposits within the wall of the bladder.
- For patients with advanced prostate cancer, use of a luteinizing hormone-releasing hormone agonist without a peripheral androgen blocker may be beneficial in limiting anemia caused by complete androgen blockade.
- In patients with limited bone marrow reserve, blood transfusions may be the only effective treatment of anemia associated with prostate cancer.

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