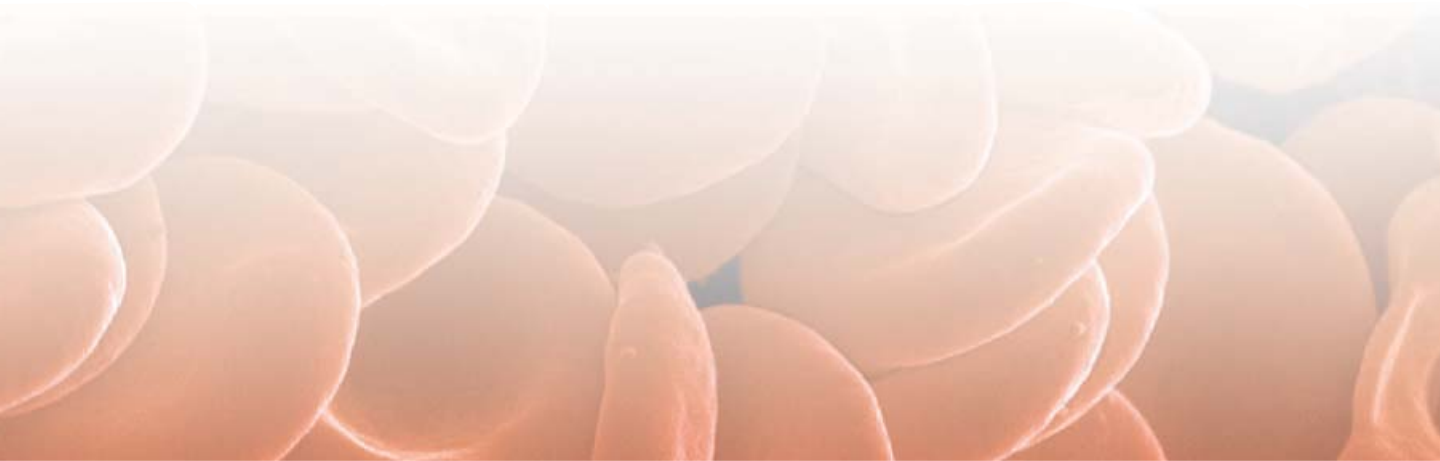
"While fatigue is the primary symptom of anemia in cancer patients, anemia can also cause a range of other symptoms…"

v Anemia & Cancer

Key Points

- Because anemia is a common complication of cancer and its treatment, all cancer patients should be assessed for anemia.
- Anemia causes debilitating symptoms, with fatigue being the most prevalent.
- Anemia may have an adverse effect on cancer outcomes.
- Erythropoietin therapy has been shown to decrease transfusion requirements, improve quality of life, and improve cancer treatment outcomes.



Multifactoral Causes of Cancer-Related Anemia

Many factors contribute to cancer-related anemia, some associated with the progression of cancer and others associated with cancer therapy.[1] Factors likely to increase the risk of anemia include the type, stage, and duration of disease; treatment regimen and intensity; presence of infection; and the need for surgical intervention.[1]

Disease-Related Anemia

Anemia related to the progression of cancer can result from activation of the immune and inflammatory systems, leading to an increased release of cytokines, including tumor necrosis factor, interferon-gamma, and interleukin-1.[2,3] At least three mechanisms participate in the cytokine-mediated failure of erythropoiesis: impaired iron utilization, suppression of erythroid progenitor cell differentiation, and inadequate erythropoietin production.[2] Patients with cancer have been shown to have inappropriately low levels of circulating erythropoietin for their degree of anemia,[4] which could reflect a disruption of homeostatic mechanisms due to the inflammatory state associated with malignancy.[5] In addition, the life span of red blood cells is shortened in cancer-related anemia, and production of new cells cannot compensate for the shortened survival time.[2] Bleeding from the tumor bed or bleeding due to systemic coagulopathy may also contribute to anemia in these patients.[6]

The prevalence of anemia due to cancer progression varies based on the definition of anemia and the type of cancer involved. A survey of 38 studies, most of which evaluated anemia prevalence in cancer patients before treatment, found that the prevalence ranged from 5% (prostate cancer) to as high as 90% (multiple myeloma).[7] The prevalence of anemia appears to be especially high in patients with uterine-cervical cancers, advanced multiple myeloma, and those suffering from cancer-related renal impairment.[8,9]

Treatment-Related Anemia

In contrast to disease-related anemia, anemia due to chemotherapy or radiation therapy results mainly from myelosuppression, but it can also occur because of the destruction of red blood cells due to treatment.[10] At least one chemotherapy drug, cisplatin, appears to blunt erythropoietin production and cause prolonged anemia,[3] and repeated cycles of this and other types of chemotherapy may cumulatively impair erythropoiesis.[6]

A broad review of clinical trials noted that mild anemia after chemotherapy can occur in 100% of patients, and the incidence of more severe anemia can reach 80%.[11] The incidence of chemotherapy-related anemia varies depending on tumor type and regimen. Cisplatin and etoposide, a combination frequently used for the treatment of non-small-cell lung cancer, causes severe anemia in 16% to 55% of patients; however, treatment of advanced colorectal cancer with 5-fluorouracil and leucovorin causes severe anemia in only 2% to 5% of patients.[12]

Radiation therapy can also increase the incidence of anemia in cancer patients. In one study of nearly 600 randomly selected cancer patients, radiation therapy increased the overall percentage of ane-

mic patients from 41% before therapy to 54% after therapy.[8] In patients with lung/bronchus cancer, radiation increased the prevalence from 55% to 77%, and in patients with colorectal cancer, the prevalence increased from 44% to 63%.[8]

Table 5-1.

CAUSES OF CANCER-RELATED ANEMIA

Neoplastic process: chronic anemia of cancer
Chemotherapy and radiation therapy
Intercurrent infections
Clonal disorders of hematopoiesis
Gastrointestinal blood loss
Autoimmune hemolysis
Microangiopathy
Excessive marrow fibrosis and displacement
Iron, folate, vitamin B_{12} deficiency
Renal impairment

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Symptoms of Anemia

Approximately 75% of all cancer patients report symptoms of fatigue,[13,14] which can present as weakness, listlessness, low energy, trouble starting and finishing tasks, and the need to sleep during the day.[9,14-17] While fatigue is the primary symptom of anemia in cancer patients, anemia can also cause a range of other symptoms, including palpitations, impaired cognitive function, nausea, reduced skin temperature, impaired immune function, dizziness, headache, chest pain, shortness of breath, and depression.[14]

Clinical Consequences of Anemia

Fatigue and Decreased Quality of Life

Cancer-related fatigue can have a profound effect on quality of life (QOL) for cancer patients. One study found that fatigue is associated with significant physical, emotional, psychological, and emotional consequences, which impact virtually every aspect of daily life.[13] Vogelzang and colleagues, in a Fatigue Coalition survey of more than 400 cancer patients, noted that 61% of the patients reported that fatigue adversely affected their lives more than cancer-related pain.[18]

Work schedules are also affected, with Curt reporting that employed cancer patients take an average of 4.2 days off per month during or immediately after treatment, due to fatigue.[13] In one study, none of the patients with low-level fatigue and high Hb levels reported the inability to work, whereas 30% of patients with low Hb levels reported that they could not work, even though they did not complain of more fatigue relative to the rest of the patient groups.[14] Other side effects associated with anemia, although not necessarily with fatigue, include dizziness, headaches, dyspnea, chest pain, and decreased libido.[14]

Increased Mortality

Anemia also increases the risk of mortality in cancer patients. In a systematic review of 60 papers, Caro and colleagues examined the survival of cancer patients according to either Hb levels or the presence of anemia and found that the relative risk of death varied by cancer type. Overall, the presence of anemia in cancer patients increased the relative risk of death by 65% (Adjusted HRR, 1.65; 95% CI, 1.54-1.77). Anemic patients with head and neck carcinoma, and those with lymphoma experienced the greatest risk, 75% (Adjusted HRR, 1.75; 95% CI, 1.37-2.23) and 67% (Adjusted HHR, 1.67; 95% CI, 1.54-1.77), respectively.[19]

Decreased Treatment Efficacy

One of the ways anemia increases mortality is by influencing treatment efficacy. Anemia influences response to radiation therapy because it limits the oxygen-transporting capacity of the blood and consequently tissue oxygenation. Thus, anemia can contribute to tumor hypoxia, which makes solid tumors resistant to sparsely ionizing radiation and some forms of chemotherapy.[20] Hypoxia also influences the number of cells destroyed following therapy by modulating the proliferation and cell cycle position of tumor cells.[20] In contrast, well-oxygenated tumors have a greater chance of being controlled.[21-23] Many studies have documented the association between anemia and poor outcome in cancers of the head and neck, respiratory tract, pelvis, and genitourinary organs.[24]

Pretreatment anemia has been identified in more than 40 studies as an adverse prognosticator in patients receiving radiotherapy or chemoradiation for solid tumors.[22] For example, researchers studying a group of patients with head and neck cancer receiving intra-arterial high-dose cisplatin and radiation therapy found that pretreatment Hb level was significantly predictive of complete response at primary and nodal sites, local-regional failure-free survival, and overall survival.[24] Findings of a study of more than 200 head and neck cancer patients indicated that moderate anemia was an independent prognostic factor for failure of local-regional control in squamous cell carcinoma of the head and neck treated with radiation therapy (RR, 1.6; 95% CI, 1.0-2.7).[25] A retrospective chart review of more than 600 patients with carcinoma of the cervix found that although pretreatment anemia was not a significant predictor, Hb levels ≥12 g/dL during radiotherapy were predictive of successful treatment and disease-free survival.[26]

Beneficial Effects of Anemia Management

Because of the detrimental effects of anemia on QOL and prognosis of cancer patients, treatment of anemia would be expected to improve outcomes. Findings of a number of studies have demonstrated reduced transfusion requirements and improved QOL when the anemia of cancer patients is treated with epoetin.

While transfusions are a rapid and reliable method of correcting anemia, especially in life-threatening situations, they do present risks for cancer patients. Along with allergic/febrile reactions, transfusion-associated immunosuppression may influence postoperative infection rates and long-term prognosis.[9,27,28]

A review of 22 trials of patients with treatment-related anemia, by Seidenfeld and colleagues, found that epoetin therapy reduced the percentage of patients transfused by 7% to 47%.[29] In a controlled trial of 375 patients, Littlewood and colleagues noted significantly decreased transfusion requirements in patients receiving nonplatinum chemotherapy and epoetin compared to those receiving only the chemotherapy (P = 0.006).[30] Dunphy and colleagues found a 50% reduced need for transfusions in patients treated with epoetin compared to those not receiving the therapy, in a randomized controlled study of 30 patients with advanced head and neck or lung carcinoma who were

treated with paclitaxel and carboplatin.[31] The effect appears to occur regardless of whether patients are undergoing chemotherapy. According to findings by Quirt and colleagues, when 401 anemic patients were administered epoetin, the need for transfusions decreased, both in the 218 patients receiving chemotherapy and the 183 patients not receiving chemotherapy.[32]

Epoetin treatment has also been found to improve QOL in cancer patients. In a randomized study of 180 patients with anemia due to hormone-refractory prostate cancer, Johansson and colleagues observed that epoetin therapy improved QOL, physical functioning, and fatigue in many of the treated patients.[33] Quirt and colleagues found that, regardless of whether patients were receiving chemotherapy, Hb levels increased with administration of epoetin, and these increases were positively correlated with improved QOL.[32] Glaspy and colleagues reported that mean energy level increased by 38%, activity increased by 32%, and overall QOL increased by 24% in over 1,000 patients with nonmyeloid malignancies who received 4 months of epoetin therapy while undergoing chemotherapy.[34] In their controlled study of 375 patients receiving nonplatinum chemotherapy, Littlewood and colleagues determined that compared with those receiving placebo, the patients treated with epoetin showed increased Hb levels (P <0.001) and improvement in a number of QOL domains, including energy level, fatigue, and ability to perform daily activities (P <0.01).[30] Similarly, Demetri and associates reported that Hb values increased and were associated with improved activity level, energy, and overall well-being in patients receiving epoetin therapy.[35]

Treatment of anemia may also improve response to treatment. Frommhold and colleagues, in a study of nearly 900 head and neck cancer patients, found that anemic patients treated with epoetin and undergoing radiotherapy experienced better locoregional tumor control than patients not receiving epoetin.[36] Similarly, Glaser and colleagues have noted improved response to chemoradiation for oral or oropharyngeal squamous cell carcinoma when patients are treated with epoetin.[37,38] A Phase III trial is currently being conducted by the Gynecologic Oncology Group to evaluate the efficacy of maintaining Hb levels above 12 g/dL with erythropoietin versus above 10 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer.[39] The Radiation Oncology Therapy Group is also conducting a randomized Phase III trial, assessing the effect of erythropoietin on local-regional control in anemic patients treated with radiotherapy for squamous cell carcinoma of the head and neck.[40]

While darbepoetin alfa (novel erythropoiesis stimulating protein, NESP) has been approved by the Food and Drug Administration (FDA) for treating anemia in patients with chronic kidney disease (CKD), findings of clinical trials have demonstrated positive results in cancer patients as well. As has been shown in patients with CKD, Heatherington and colleagues found that the half-life of darbepoetin alfa is three times greater than that of epoetin in cancer patients, suggesting that this erythropoietic agent can

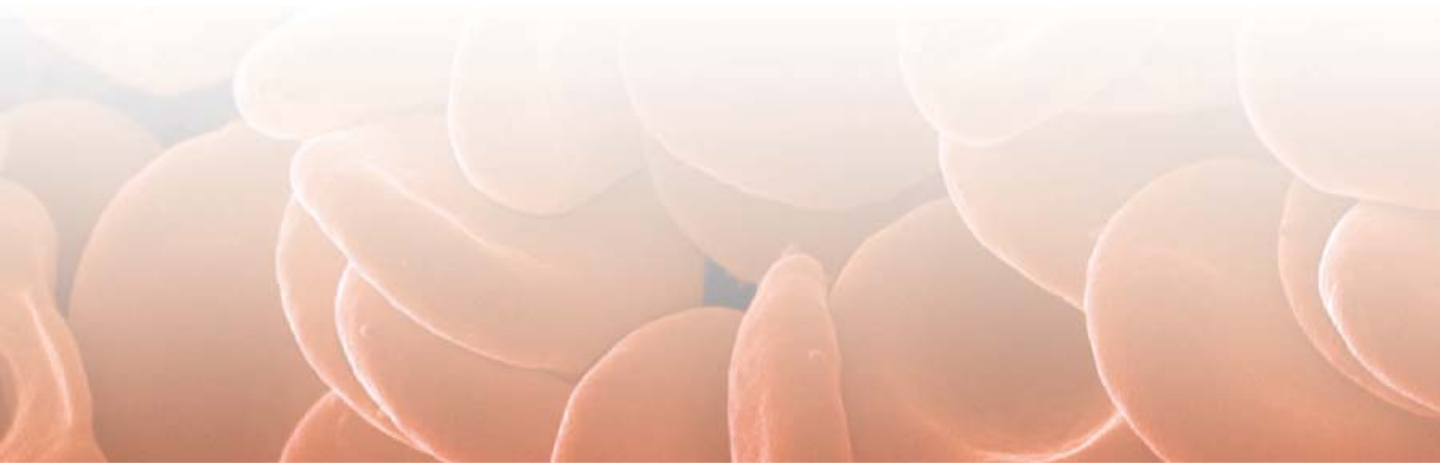
be administered less frequently.[41]

In 89 anemic patients with nonmyeloid malignancies who were not receiving chemotherapy, Smith and colleagues found that darbepoetin alfa was well tolerated. Increasing doses corresponded with increased efficacy, and most patients responded to treatment.[42] In a more recent dosing study, Smith and colleagues evaluated 96 patients with nonmyeloid malignancies and chronic anemia, who were not receiving chemotherapy or radiation therapy. Darbepoetin alfa again was found to be safe and effective, with increased doses resulting in shorter time to response. In patients who received 6.75 mcg/kg every 3 (Q3W) or 4 (Q4W) weeks, serum concentrations of darbepoetin alfa were maintained above baseline for up to 3 to 4 weeks post-dose, and the terminal half-life was about 60 hours.[43]

Glaspy and colleagues assessed the efficacy of darbepoetin alfa in 107 cancer patients with solid tumors who were receiving multicycle chemotherapy. In three dose cohorts, the medication was found to be well tolerated, safe, and effective in increasing Hb levels.[6] In a 12-week study involving 122 anemic patients with solid tumors who were receiving multicycle chemotherapy, the same researchers recently compared the efficacy of darbepoetin alfa to epoetin alfa. Patients were randomized to receive darbepoetin alfa in a 4-week front load phase followed by an 8-week maintenance phase that involved less frequent dosing or epoetin alfa at 40,000 units per week as a starting dose. After 12 weeks, 61% of patients treated with darbepoetin alfa responded to treatment compared to 49% of the patients treated with epoetin alfa, even when doses were increased to 60,000 units per week for those patients whose initial responses were inadequate. Darbepoetin doses were not increased for patients who did not respond.[44]

Kotasek and colleagues recently evaluated the efficacy of darbepoetin alfa administered Q3W or Q4W, the same time frequency of most chemotherapy regimens. Data on 414 anemic patients with solid tumors on chemotherapy, who participated in the placebo-controlled trial, indicate that darbepoetin alfa can be safely and effectively administered very infrequently, allowing once per cycle dosing in patients receiving chemotherapy.[45]

Darbepoetin alfa is currently undergoing FDA review for use in the treatment of anemia in cancer patients receiving chemotherapy.



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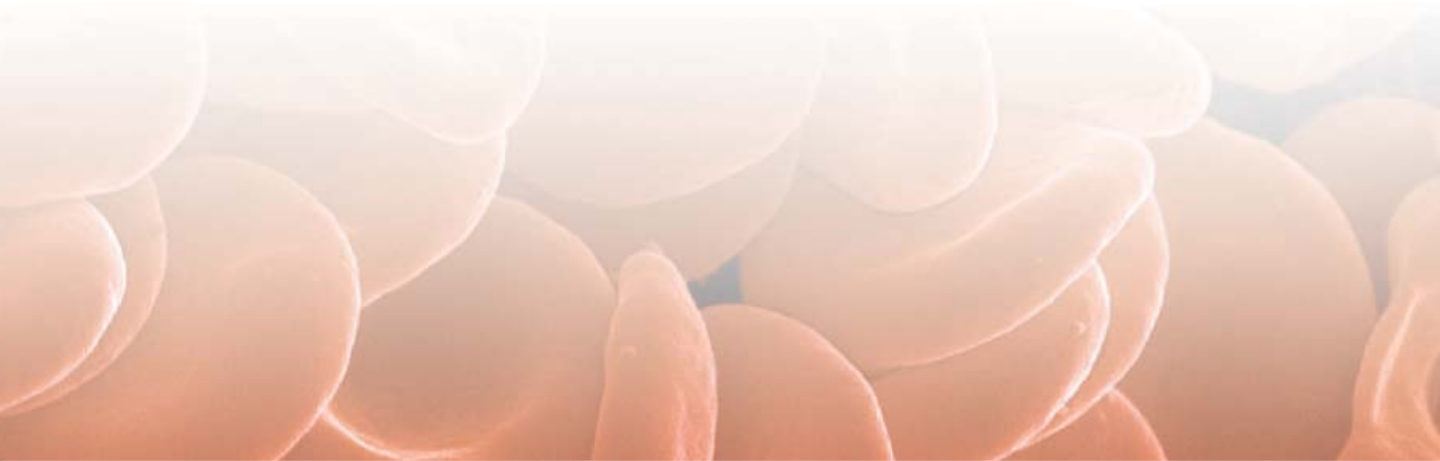

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