Anemia is a decrease in circulating red blood cells that contributes to a complex group of symptoms. Anemia may be present in more than half of all patients with cancer but often is assessed, documented, prevented, and treated inadequately. Individuals with cancer are living longer, and the number of cancer treatment options provided at various points in the cancer continuum is growing; however, many treatments contribute to anemia. Because anemia can develop from multiple causes, treatment must be tailored to the underlying etiology. Cancer-related anemia can significantly affect therapeutic outcomes and patients’ quality of life. Therapeutic interventions may include blood transfusions, administration of recombinant human erythropoietin, and interventions to support patient symptoms, most significantly, fatigue. Oncology nurses play a central role in risk assessment, symptom management, treatment planning, and evaluation and therefore must understand the etiology and physiology of cancer-related anemic states as well as evidence-based interventions to ensure optimal outcomes.

At a Glance

✦ Anemia often is assessed, documented, prevented, and treated inadequately.
✦ Cancer-related anemia can significantly affect therapeutic outcomes and patients’ quality of life.
✦ Oncology nurses play a central role along the continuum of care of patients experiencing cancer-related anemia.
Causes of Cancer-Related Anemia

Anemia is defined as a decrease in the volume of circulating red blood cells (RBCs) or the concentration of hemoglobin resulting in the body’s diminished ability to carry oxygen to tissues (Lynch, 2006d). The causes of anemia may be multifactorial, especially in patients with cancer undergoing multiple and prolonged treatment regimens. Anemia may result from decreased RBC production, increased RBC destruction, decreased circulating RBCs, or a combination of those factors, as well as other complicating reasons (e.g., poor dietary intake of iron), which often is the case in patients with cancer (Loney & Chernecky, 2000). Inadequate production of RBCs may result from defects in erythropoietin-producing cells, DNA synthesis, hemoglobin synthesis, bone marrow suppression, or renal failure (Lynch, 2006d). RBC destruction is caused by many factors such as intrinsic factors (e.g., enzyme deficiencies) or cancer-related extrinsic destruction by chemotherapeutic agents (e.g., antimetabolites), the malignancy itself stimulating an autoimmune hemolysis (e.g., chronic lymphocytic leukemia), or inflammatory cytokines produced by the malignancy destroying RBCs (e.g., tumor necrosis factor) (Loney & Chernecky; Lynch, 2006d; Worrall, Tompkins, & Rust, 1999). Decreased circulating RBCs can result from acute hemorrhage or cancer-related coagulopathies as in disseminated intravascular coagulation. In patients with cancer, compounding factors such as deficiencies in iron, vitamin B₁₂, and folate present risks for decreased production and loss of circulating RBCs (Loney & Chernecky).

The etiology of anemia often is classified according to the size of the RBC, which is determined by evaluation of the mean corpuscular volume laboratory data. Anemia may be classified as microcytic, normocytic, and macrocytic (Lynch, 2006d) (see Table 1). Other classifications may be based on RBC morphology, including the amount of pigment, noted by the mean corpuscular hemoglobin (e.g., hypochromic, normochromic), or by the reticulocyte count, which delineates the productive capacity of the bone marrow to meet the RBC requirements of the body. A low reticulocyte count demonstrates decreased RBC production, whereas a high reticulocyte count indicates increased RBC destruction (Lynch, 2006d).

### Microcytic Anemia

Two common causes of microcytic anemia in patients with cancer are iron deficiency or comorbid chronic disease states. In microcytic anemia, the RBC is small in size (i.e., mean corpuscular volume < 80 fl). In patients with iron deficiency, microcytic anemia is caused by insufficient iron for hemoglobin synthesis. Iron deficiency anemia is the most common cause of anemia worldwide, occurring frequently in young children, pregnant women, and older adults (Lynch, 2006c; Worrall et al., 1999). In patients with cancer, the most frequent causes of iron deficiency are inadequate absorption (e.g., gastrectomy), excessive loss of iron because of blood loss (i.e., uterine, gastrointestinal, or genitourinary tract bleeding) (Lynch, 2006c), or other cancer-related effects such as anorexia resulting in poor dietary intake of iron (Loney & Chernecky, 2000). Differential diagnoses for iron deficiency microcytic anemia in patients with cancer include other hematologic disorders such as thalassemia minor and sideroblastic anemia (Lynch, 2006c).

Malignancies and other conditions such as chronic infection, inflammatory conditions, and congestive heart failure contribute to a common set of factors resulting in anemia and are referred to as anemia of chronic disease (ACD). ACD is triggered by immune and inflammatory cytokines that are common to those conditions, specifically tumor necrosis factor, interleukin-1, and interferon (Cella et al., 2003). Reduced erythropoietin production results from inhibition of RBC precursors in the bone marrow, impaired iron uptake by developing RBCs, or erythropoietin inadequately released from the kidneys (Lynch, 2006a). Chronic infections decrease the stem cell pool in addition to reducing the body’s response to erythropoietin stimulation (Loney & Chernecky, 2000).

The reticulocyte count is the productive capacity of the bone marrow to meet the RBC requirements of the body. Patients with ACD have a low reticulocyte count, indicating a hypoproliferative state. Differential diagnoses for microcytic ACD in patients with cancer include other hematologic disorders such as aplastic anemia, bone marrow suppression caused by myelodysplasia or chemotherapy, and anemia resulting from chronic renal failure (Lynch, 2006a).

### Normocytic Anemia

In its early stages, ACD may present as normocytic anemia, a state in which RBCs are normal in size. Classification by RBC

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### Table 1. Classifications of Common Cancer-Related Anemias

<table>
<thead>
<tr>
<th>ANEMIA TYPE</th>
<th>DESCRIPTION</th>
<th>DIFFERENTIAL DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcytic</td>
<td>Decreased mean corpuscular volume (MCV) (&lt; 80 fl) Red blood cells (RBCs) small in size</td>
<td>Iron deficiency Anemia of chronic disease Thalassemia minor Sideroblastic anemia</td>
</tr>
<tr>
<td>Normocytic</td>
<td>Normal MCV (80–100 fl) RBCs normal in size</td>
<td>Anemia of chronic disease Hemolytic anemia Aplastic anemia Renal failure</td>
</tr>
<tr>
<td>Macrocytic</td>
<td>Increased MCV (&gt; 100 fl) RBCs large in size</td>
<td>B₁₂ deficiency Folate deficiency Myelodysplastic syndromes</td>
</tr>
<tr>
<td>Low reticulo-cyte count</td>
<td>Decreased RBC production &lt; 0.5%–1.5% of erythrocytes</td>
<td>Anemia of chronic disease Aplastic anemia Iron deficiency Vitamin B₁₂ deficiency Folate deficiency Bone marrow suppression or infiltration</td>
</tr>
<tr>
<td>High reticulo-cyte count</td>
<td>Increased RBC destruction &gt; 0.5%–1.5% of erythrocytes</td>
<td>Hemolysis Chemotherapy-induced Autoimmune</td>
</tr>
</tbody>
</table>

*Note. Based on information from Loney & Chernecky, 2000; Lynch, 2006d.*
size is dependent on the type and stage of the anemia. Patients with cancer often present with ACD and chemotherapy-induced anemia or iron deficiency depending on the disease stage and treatment. Hemolytic anemias are normocytic and most commonly are drug induced or result from renal failure. Chemotherapy or radiation therapy may directly decrease RBC production because of treatment-induced bone marrow suppression causing depletion of pluripotent stem cells. The metabolic effects of destroying RBCs may be compounded by physical factors such as displacement of bone marrow by tumor metastases or fibrosis or, rarely, damage by bone marrow necrosis (Smith & Tchekmedyian, 2002). Severe catabolism associated with cancer also may impair protein production, rendering the bone marrow unable to effectively produce an adequate number of RBCs (Smith & Tchekmedyian) yet those present remain normal in size.

The processes of erythropoietin production and erythropoiesis are essential in stimulating the bone marrow for RBC production and maturation. A normal feedback loop occurs when hypoxia in the renal cells triggers release of erythropoietin from the bone marrow (Loney & Chernecky, 2000). As a result, decreased RBC production can be caused by kidney damage related to a tumor or nephrotoxic chemotherapy or, rarely, radiation renal injury, as well as other coexisting causes of renal insufficiency such as end-stage renal disease (Worrall et al., 1999).

Other causes of hemolytic anemia in patients with cancer may include autoimmune hemolysis (e.g., cold agglutinin antibodies), enzyme deficiencies (e.g., glucose-6-phosphate dehydrogenase), or RBC destruction by tumor (e.g., non-Hodgkin lymphoma), chemotherapeutic agents (e.g., cisplatin), total body irradiation (e.g., bone marrow transplant), or risks associated with cancer and its treatment (e.g., disseminated intravascular coagulation). In addition, nonchemotherapeutic medications common to cancer protocols can contribute to anemia (e.g., lorazepam) (Loney & Chernecky, 2000; Lynch, 2006d; Worrall et al., 1999).

Macrocytic Anemia

Abnormal maturation of RBCs contributes to macrocytic or large cells (> 100 fl), such as in vitamin B$_{12}$ and folate deficiencies which interfere with DNA synthesis necessary for RBC precursors (Worrall et al., 1999). Impaired absorption of vitamin B$_{12}$ (cobalamin) may be related to deficiency of intrinsic factor secreted by the parietal cells of the stomach (e.g., total gastrectomy). Pernicious anemia is an autoimmune reaction that causes atrophy of the gastric mucosa and failure of intrinsic factor secretion (Lynch, 2006b; Worrall et al.) (see Figure 1). Vitamin B$_{12}$, or intrinsic factor deficiency causes megaloblastic, macrocytic, normochromic anemia and occurs more commonly in the sixth decade of life. It is insidious in nature because of bodily stores of vitamin B$_{12}$; yet deficiencies may occur in patients who are strict vegetarians (e.g., no dairy or meat), in those with bacterial infections of the gastrointestinal tract, or when precipitated by certain medications (e.g., cimetidine) (Lynch, 2006b; Worrall et al.). Vitamin B$_{12}$ is necessary for the metabolism of folate. Bodily stores of folate are not abundant; therefore, dietary intake (e.g., green leafy vegetables) is important. Deficiencies in folic acid may occur because of alcoholism, liver disease, malabsorption syndromes, and anorexia. In patients with cancer, medications may lead to folic acid deficiencies such as anticonvulsants (e.g., phenytoin) and folate acid antagonists (e.g., hydroxyurea, methotrexate, pemetrexed) (Worrall et al.). Differential diagnoses for macrocytic anemia include vitamin B$_{12}$ or intrinsic factor deficiency, folate deficiency, ACD, and myelodysplastic syndromes (Lynch, 2006b).

The causes and risks for CRA include iron, vitamin B$_{12}$, and folate deficiencies; the malignancy itself; treatment; inflammation; infection; comorbid disease (e.g., renal failure); and hemolysis (Worrall et al., 1999). The causes of CRA are multiple and complex and therefore require astute clinical evaluation to determine patient risk factors and the underlying etiology. A clinical guide for delineating the causes of anemia can be found in Figure 2.

**Impact of Cancer-Related Anemia**

Despite the difficulties in assessing anemia and its related symptoms, trends in the prevalence of anemia in patients with cancer have been identified. Some tumor types reportedly correlate with high rates of anemia, such as lung cancer (52%) and ovarian cancer (51%). The high incidence probably is related to the advanced age of many patients with lung cancer and the frequent use of platinum-based therapies for tumors at both sites (Gillespie, 2002). The options for multiple chemotherapy protocols are increasing and individuals with cancer are living longer after treatment; therefore, the effect of anemia on patients' quality of life and their response to treatment will continue to present challenges for healthcare professionals (Hudis, Van Belle, Chang, & Muenstedt, 2004).

**Physical and Psychosocial Impact**

The physical and psychosocial impact of undetected CRA can be profound (Loney & Chernecky, 2000). A major complication of anemia is fatigue. Anemia results in decreased oxygen delivery to tissues and, when untreated, eventually leads to a negative energy balance (Gutstein, 2001). According to patient

![Figure 1. Photomicrograph of Pernicious Anemia in Bone Marrow Cells](image)

*Note. Copyright C. James Webb/Phototake. All rights reserved. Reprinted with permission.*
Figure 2. Algorithm for Identifying the Causes of Cancer-Related Anemia


RBC—red blood cell
reports, fatigue is the most distressing symptom associated with cancer and its treatment (Mock, 2001). As cancer treatment protocols have become more dose dense and dose intensive, the risk of anemia has increased, as well as the likelihood that cancer-related fatigue will become more distressing for patients, adversely affecting their quality of life (Mock).

Fatigue is difficult to assess objectively because it is a multifactorial and multidimensional symptom with physical, emotional, and cognitive effects (Escalante et al., 2001; Von Gunten, 1999). Fatigue has been defined as “a subjective state of overwhelming sustained exhaustion and decreased capacity for physical and mental work that is unrelieved by rest” (Escalante et al., p. 1708). The significant loss of energy associated with even mild anemic states can limit patients’ ability to perform everyday activities, including work, social, and leisure activities. Fatigue also has been correlated with loss of self-esteem, anxiety, depression, and emotional stress (Escalante et al.). Severe fatigue may diminish patients’ ability to cope with cancer and its treatment. In a literature review, Von Gunten reported that correcting anemia-related fatigue correlated with at least a modest improvement in overall quality of life and energy levels.

Other disturbing symptoms that occur with anemia are caused by increased cardiac output, shunting of blood to vital organs, and peripheral vascular dilation (Cella et al., 2003; Hudis et al., 2004). Mild anemia can cause tachycardia, palpitations, and dyspnea on exertion (Loney & Chernecky, 2000). Severe anemia results in disabling fatigue states, compounds tachycardia and dyspnea, and may precipitate headaches, dizziness, mood changes, and difficulty concentrating, whereas prolonged anemia may cause insomnia, anorexia, indigestion, menstrual irregularities, and sexual dysfunction (Loney & Chernecky).

**Anemia’s Impact on Treatment and Survival**

Hypoxia, a characteristic feature of locally advanced solid tumors, has been recognized as a critical factor in promoting tumor resistance to radiotherapy, chemoradiation, and some chemotherapeutic agents (Littlewood, 2001; Shasha, 2001). In a systematic review to determine whether anemia was an independent prognostic factor for cancer survival, the overall risk of death increased by 65%, adjusting for variables, in anemic patients with cancer relative to those without anemia (Caro, Salas, Ward, & Goss, 2001).

Severe anemia may have an impact on therapies used to manage cancer. Anemia may delay surgical interventions when treatment requires preoperative correction through RBC transfusion. Similarly, low levels of hemoglobin before or during chemotherapy cycles may require dose reductions or delays in administration, resulting in a decrease in the overall treatment intensity. Tumor hypoxia also may limit the effectiveness of oxygen-dependent chemotherapy (Cella et al., 2003; Kelleher, Mattheinsen, Thews, & Vaupel, 1996).

Hemoglobin levels are reported to be a strong independent prognostic factor for tumor control by radiation therapy, with the hemoglobin level at the conclusion of therapy believed to be more important than the baseline level (Finney & Allison, 2005; Lavey, 1998). Cells that are not fully oxygenated are substantially less sensitive to the effects of ionizing radiation. The proportion of cells killed by a given dose of radiation under well-oxygenated conditions is termed oxygen enhancement ratio. Radiation biologists have hypothesized that minimally oxygenated tumor cells most distant from the capillary are relatively resistant to radiotherapy and are the most likely source of local treatment failure. In addition, anemia may increase local failure rates by exacerbating local tumor hypoxia (Caro et al., 2001; Harrison, Shasha, White, & Ramdeen, 2000). Although the link among treatment of preexisting mild anemia, local control, and cure rates for radiation therapy has not been sufficiently confirmed in randomized clinical trials, most clinicians accept the premise that anemia compromises radiotherapy and that it merits careful attention when cure or improved survival is a potential therapeutic outcome (Finney & Allison; Glaspy, 2002). Hemoglobin levels have been strongly correlated with tumor size, which may explain the poorer outcomes reported for patients with anemia receiving radiation therapy in earlier published studies (Gillespie, 2003).

**Assessment Criteria**

Assessment begins with a thorough history that identifies patients who are at risk for developing anemia or symptoms that may be changing over time such as fatigue-related lifestyle changes (Loney & Chernecky, 2000) (see Figure 3). Physical examination must include all organ systems and may reveal pallor, tachycardia, systolic ejection murmur (53 extra heart sound), shortness of breath on activity, and pedal edema (Loney & Chernecky). Careful assessment of anemia and its related symptoms is made more difficult by the lack of a standard definition of the condition, the absence of gender-specific differences in normal hemoglobin levels, and variable trigger points leading to transfusion (Gillespie, 2003). Individual assessments should evaluate current blood counts and other pertinent laboratory values (see Figure 4). Physical symptoms (e.g., pulmonary, cardiac) should be ascertained as well as changes in trends related to the findings over time. Patients who become more symptomatic, as compared with baseline values, may be experiencing an increase in the severity of anemia, even if the hemoglobin level has not decreased to very low levels.

Complicating the assessment, objective findings in symptomatic patients with a given hemoglobin value cannot be generalized to others with similar values (Gillespie, 2003). Laboratory data play a pertinent role in the assessment of anemia, and nurses should be familiar with normal ranges for the complete blood count with indexes (see Table 2). When indicated, standards of practice recommend that anemia assessment should include examination of the peripheral smear, bone marrow aspiration and biopsy (e.g., hypocellular marrow found in aplastic anemia), and serum creatinine to evaluate renal function (Earles, 2004; Lynch, 2006c).

Astute patient assessment is vital to differentiate anemia-related symptoms such as fatigue and mood changes from other major diagnoses (e.g., depression, chemotherapy-induced cognitive changes). The underlying cause of anemia must be determined for the optimal intervention to be designed. Concomitant processes, such as nutritional deficiencies, inflammation, infection, hemolysis, blood loss, and other diagnoses in the context of cancer, should be evaluated as well as information about the impact of current or previous myelosuppressive therapy (Groopman...
Multiple causes of anemia exist, and treatment is tailored to the cause. The degree of anemia is not always reflective of the severity of the causative disorder; therefore, careful and thorough assessment, including attention to patterns that patients experience, is critical in anemia treatment (Gillespie, 2003; Groopman & Itri; Tavio, Milan, & Tirelli, 2002). Quantitative assessment scales such as the Anemia Subscale of the Functional Assessment of Cancer Therapy and the Brief Fatigue Inventory can be used to assess the impact of fatigue on patients’ daily activities. Nurses also can incorporate a 0–10 numeric rating scale or a descriptive scale (e.g., mild, medium, severe) into their patient assessments (Earles, 2004).

Symptom Management

Correction or management of the underlying etiology in patients with documented anemia is the optimal outcome (Gillespie, 2003; Groopman & Itri; Tavio et al., 2002). Once the source of anemia has been determined, treatment can be initiated. Supportive interventions include transfusion therapy, erythropoiesis-stimulating therapies, iron supplementation, nutrition, and patient education (see Figure 5). Because multiple causes of anemia may be present in an individual, more than one therapy often is necessary.

Evidence-based guidelines for the treatment of anemia in patients with cancer have been established (Earles, 2004). Joint practice guidelines were adopted by the American Society of Clinical Oncology and the American Society of Hematology in 2002 (Rizzo et al., 2002), and the National Comprehensive Cancer Network (NCCN) published an updated version of guidelines in 2007. The standards of care for CRA must be incorporated into clinical practice to ensure consistency and benefit for patients (Berger, 2005).

Transfusion Therapy

The NCCN (2007) guidelines defined levels of hemoglobin to guide interventions—mild anemia (10–11 g/dl), moderate anemia (8–10 g/dl), and severe anemia (< 8 g/dl). When clinical symptoms warrant immediate correction, transfusion therapy is appropriate (Earles, 2004). Packed RBCs usually are administered for a hemoglobin level less than 8 g/dl, raising the level of hemoglobin quickly to ensure adequate oxygen-carrying capacity to vital organs and improving overall clinical status (Von Gunten, 1999). Symptoms of anemia generally are relieved and quality-of-life data support that optimal improvement occurs when the hemoglobin level ranges from 11–12 g/dl (Earles). Although the blood supply in the United States is considered extremely safe, RBC transfusion is not without accompanying risk and patients often are concerned about the hazards (Gillespie, 2002, 2003). The potential for transfusion reactions (e.g., allergic, febrile, hemolytic), as well as other possible risks (e.g., alloimmunization, immunosuppression,
iron or circulatory overload, transfusion-related acute lung injury, transfusion-transmitted infectious agents), should be considered prior to initiation of transfusion therapy (Gillespie, 2002, 2003; Perrotta & Snyder, 2001). Some patients may have religious beliefs prohibiting the use of blood or blood products (Gillespie, 2003).

Not only does transfusion therapy rapidly correct anemia and related symptoms, it reduces delays in cancer treatment because of anemia. However, quantifiable disadvantages must be considered, including supply issues, expenses associated with blood products and their administration, and the inconvenience for patients undergoing several hours of administration. The risks and benefits of transfusion therapy must be weighed carefully in each situation (Buchsel, Murphy, & Newton, 2002; Groopman & Itri, 1999) and transfusion of RBCs should be initiated only if anemia is so severe that inadequate time exists to permit the use of an erythropoiesis-stimulating therapy (Gillespie, 2003) or in cases of anemia that are not responsive to iron, vitamin B₁₂, folate, or dietary supplementation.

**Erythropoiesis-Stimulating Therapies**

Erythropoietin is a naturally occurring hormone produced by the kidneys to regulate RBC production and specifically acts at the colony-forming unit-erythroid of the bone marrow to promote erythroid stem cell development into mature circulating erythrocytes (Buchsel et al., 2002). The production of erythropoietin is regulated by a feedback loop in which the kidney senses decreased oxygen or tissue hypoxia, decreased arterial oxygen, anemia, or increased hemoglobin affinity and releases erythropoietin (Buchsel et al.; Groopman & Itri, 1999; Tong & Nissenson, 2001).

With advances in recombinant DNA technology and the ability to manufacture hematopoietic growth factors, the introduction of rHuEPO (epoetin alfa) in the 1990s represented a significantly new approach to treatment and potential reduction in CRA and other conditions, such as chronic renal failure, zidovudine-treated patients with HIV, and patients with anemia undergoing elective, noncardiac, nonvascular surgery (Buchsel et al., 2002). Epoetin’s mechanism of action and its immunologic and hematologic properties are equivalent to those of endogenous erythropoietin (Amgen Inc., 2006b; Faulds & Sorkin, 1989).

In patients whose endogenous erythropoietin levels are abnormally low considering the degree of anemia experienced, the administration of exogenous erythropoietin may be beneficial. Conversely, if endogenous levels of erythropoietin are adequate, the addition of exogenously administered erythropoietin may be of little help in alleviating the anemia (Gillespie, 2003). For example, in patients with myelodysplasia, erythropoietin levels less than 200 μU/ml are predictive of insensitivity to epoetin (Earles, 2004). Other causes of low response include vitamin deficiencies, decreased iron stores, or infectious processes (Buchsel et al., 2002).

Prior to starting any patient on an erythropoietin-stimulating therapy, NCCN (2007) has recommended a thorough evaluation of CRA to rule out nutritional deficiencies of vitamin B₁₂, iron, and folate, in addition to assessing for hemolysis (e.g., hemoglobin electrophoresis) and evidence of gastrointestinal bleeding (e.g., guaiac testing). Other pertinent laboratory testing must be carried out to identify a noncancer- or nontreatment-related cause of anemia because the underlying cause must become the initial focus of treatment (e.g., normocytic anemia caused by hypothyroidism).

**Epoetin alfa**: Epoetin alfa (Procrit®, Ortho Biotech Products, LP; Epogen®, Amgen Inc.) was approved by the U.S. Food and Drug Administration (FDA) in 1993 for the treatment of anemia in patients with nonmyeloid malignancies (Earles, 2004). Epoetin alfa stimulates the division and differentiation

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**Table 2. Evaluation of Laboratory Data for Cancer-Related Anemias**

<table>
<thead>
<tr>
<th>LABORATORY TEST</th>
<th>NORMATIVE VALUESᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell count</td>
<td></td>
</tr>
<tr>
<td>Men: 4.7–6 million/mcl</td>
<td></td>
</tr>
<tr>
<td>Women: 4.2–5.4 million/mcl</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>Men: 13.5–18 g/dl</td>
<td></td>
</tr>
<tr>
<td>Women: 12–16 g/dl</td>
<td></td>
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<tr>
<td>Hematocrit</td>
<td></td>
</tr>
<tr>
<td>Men: 42%–52%</td>
<td></td>
</tr>
<tr>
<td>Women: 37%–47%</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td></td>
</tr>
<tr>
<td>80–100 fl</td>
<td></td>
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<tr>
<td>Mean corpuscular hemoglobin</td>
<td></td>
</tr>
<tr>
<td>27–31 pg/cell</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration</td>
<td></td>
</tr>
<tr>
<td>30%–37%</td>
<td></td>
</tr>
<tr>
<td>Red cell distribution width</td>
<td></td>
</tr>
<tr>
<td>11.5%–14%</td>
<td></td>
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<tr>
<td>Reticulocyte count</td>
<td></td>
</tr>
<tr>
<td>0.5%–1.5% of erythrocytes</td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td></td>
</tr>
<tr>
<td>Men: 20–300 ng/ml</td>
<td></td>
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<tr>
<td>Women: 15–120 ng/ml</td>
<td></td>
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<tr>
<td>Serum iron</td>
<td></td>
</tr>
<tr>
<td>Men: 75–175 ug/dl</td>
<td></td>
</tr>
<tr>
<td>Women: 65–165 ug/dl</td>
<td></td>
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<tr>
<td>Total iron-binding capacityb</td>
<td></td>
</tr>
<tr>
<td>250–450 μg/dl</td>
<td></td>
</tr>
<tr>
<td>Serum erythropoietin level</td>
<td></td>
</tr>
<tr>
<td>Men: 17.2 μU/ml</td>
<td></td>
</tr>
<tr>
<td>Women: 18.8 μU/ml</td>
<td></td>
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<tr>
<td>Serum transferrin</td>
<td></td>
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<tr>
<td>200–400 mg/dl</td>
<td></td>
</tr>
<tr>
<td>Coomb’s test (direct or indirect)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Serum B₁₂</td>
<td></td>
</tr>
<tr>
<td>190–1,100 pg/ml</td>
<td></td>
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<tr>
<td>Serum folate</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.5 ng/ml</td>
<td></td>
</tr>
<tr>
<td>Sedimentation rate</td>
<td></td>
</tr>
<tr>
<td>41%–54%</td>
<td></td>
</tr>
</tbody>
</table>

ᵃ Range of normal laboratory values is dependent on institutional guidelines.

ᵇ The National Comprehensive Cancer Network (2007) guidelines have suggested iron studies prior to erythropoietic therapy to ensure adequate iron stores.

**Note.** Based on information from Loney & Chernecky, 2000; Portenoy & Itri, 1999.
of erythrocyte stem cells in the bone marrow, resulting in the release of reticulocytes into the blood stream in 7-10 days where they mature into erythrocytes. The process of increasing the hemoglobin takes two to six weeks (Wilkes & Barton-Burke, 2005).

NCCN (2007) recommended beginning treatment with epoetin alfa using either 150 U/kg subcutaneously three times weekly or 40,000 units weekly. Doses are titrated up to 300 units/kg three times weekly or 60,000 units every week if the hemoglobin has not risen by at least 1–2 g/dl after four weeks (Amgen Inc., 2006b; Ortho Biotech Products, LP, 2006). Doses are reduced by 25% if the hemoglobin increases by more than 1 g/dl in a two-week period, and therapy is held if hemoglobin exceeds 12 g/dl (NCCN).

Erythropoietin has been shown to raise the mean hematocrit in patients with chemotherapy and CRA, independent of tumor type or disease response, significantly improving energy levels and quality of life (Demetri, Kris, Wade, Degos, & Cell, 1998; Gabrilove et al., 2001; Glaspv, et al., 1997). NCCN (2007) guidelines also recommended that prophylactic rhHuEPO be administered in asymptomatic patients with known risk factors (e.g., history of blood transfusions) or in any symptomatic patients (e.g., fatigue). Administration of epoetin alfa early in cancer therapies with known myelosuppressive risk may prevent adverse effects on clinical outcomes, but continued research is needed to identify the role of prophylactic use of erythropoietin therapy across different tumor types and treatment modalities (Earles, 2004; Gillespie, 2003; Mercadante et al., 2000).

Darbepoetin alfa: A novel erythropoiesis-stimulating agent for CRA is darbepoetin alfa (Aranesp®, Amgen Inc.). Darbepoetin alfa has a mechanism of action similar to rHuEPO, but it is biochemically distinct with a half-life two to three times longer than that of rhHuEPO, as demonstrated in patients with chronic renal failure (Gillespie, 2003; Vanrenterghem, Barany, & Mann, 1999). The agent has demonstrated equivalent efficacy in maintaining hemoglobin levels when administered as a single weekly injection instead of the two to three weekly injections required for rhHuEPO (Maccougall, 2000). Darbepoetin alfa given every two weeks also has been shown to be as effective as weekly dosing of the drug (Vanrenterghem et al.).

The FDA approved darbepoetin alfa in 2002 for chemotherapy-induced anemia in patients with nonmyeloid malignancies (Gillespie, 2003). Current NCCN (2007) recommendations include initiating therapy at 2.25 mcg/kg every week or a fixed dose of 500 mcg every three weeks. Alternative fixed dosing of 100 mcg every week, 200 mcg every two weeks, or 300 mcg every three weeks are noted as well with suggested titrations for poor response (Amgen Inc., 2006a; NCCN).

The dose of 200 mcg every two weeks has been compared to epoetin alfa 40,000 units every week. At those doses, darbepoetin alfa and epoetin alfa appeared to have similar effectiveness in terms of hematopoietic response and decrease the need for blood transfusions (Herrington et al., 2005). Less frequent dosing of darbepoetin alfa has cost-effective and quality-of-life advantages. Administration every three to four weeks reduces drug costs as well as the nursing time needed to prepare, administer, and monitor the medication’s effects. The long half-life of darbepoetin alfa may allow the medication to be synchronized with chemotherapy cycles, reduce patient office visits, enhance patient compliance (Demetri, 2001; Earles, 2004; Gillespie, 2003), and decrease patient and caregiver burden (Koopman & Iakiri, 2005; Longfield, Gebhart, & Hayward, 2005).

**Risks Associated With Erythropoiesis-Stimulating Therapies**


First, the revised package inserts recommended dosing interruption and/or modification based on hemoglobin levels for patients receiving growth factor support related to cancer chemotherapy. Hemoglobin levels should not exceed 12 g/dl for either therapy. The recommendations resulted from investigational studies conducted outside of the United States, where patients with cancer were treated to high hemoglobin target levels, beyond the correction of anemia. The studies permitted or required dosing with either erythropoiesis-stimulating therapy to achieve hemoglobin levels more than 12 g/dl. An increased frequency of adverse patient outcomes, including increased mortality and thrombotic vascular events, was reported in the studies (Amgen Inc., 2006b; Ortho Biotech Products, LP, 2006).

Second, the FDA warned that, although rare, the presence of neutralizing antibodies to erythropoietin have caused serious adverse reactions, including pure red cell aplasia and severe anemia compounded by other cytopenias (Amgen Inc., 2005). Patients with chronic renal failure are most susceptible to the reactions; however, oncology nurses must be aware of the risks and monitor for signs and symptoms indicative of increasing anemia (e.g., increasing fatigue, pallor). Because of the rapid proliferation of stem cells with the therapies, oncology nurses should be aware of other possible adverse reactions. Both medications are contraindicated in patients with uncontrolled hypertension or any patient with a known hypersensitivity to substances in the product (e.g., mammalian cell-derived products, human albumin) (Buchel et al., 2002; Gillespie, 2003). Finally, additional adverse reactions seen in patients treated with darbepoetin alfa have included pulmonary embolism, deep vein thrombosis, and edema (Amgen Inc., 2006a; Gillespie, 2005).

**Iron supplementation:** Iron supplementation may be required in combination with erythropoiesis-stimulating therapies to treat anemia effectively (NCCN, 2007), and supplementation also may reduce the total amount of rhHuEPO needed to correct hemoglobin levels. The transport of iron is necessary for the process of erythropoiesis. Inadequate use and transport of iron, termed functional iron deficiency, are the most common causes of an inadequate response to rhHuEPO among patients with chronic renal failure (Feeiders et al., 1998; Gillespie, 2002), and functional iron deficiency also may be an important factor in chronic anemia in cancer. NCCN, the American Society of Clinical Oncology, and the American Society of Hematology guidelines advised that iron studies be carried out periodically.
for all patients receiving erythropoietic therapy (Rizzo et al., 2002), and Medicare guidelines require that all patients receiving chemotherapy have iron studies carried out prior to treatment initiation (Gaits, Shaftic, & Terlizzi, 2005; Miskin & Hoechner, 2005). Iron supplementation may be given orally or via IV, although significant gastrointestinal discomfort and potential noncompliance can result from oral administration (Glaspy & Cavill, 1999). IV iron supplementation, however, can be inconvenient and costly and is associated with significant adverse events such as anaphylaxis. Standardization of laboratory monitoring and documentation of iron and folate supplementation, as well as patient outcomes, continue to be challenges in clinical settings (Gaits et al.).

Patient Education

Educating patients with CRA complements adjuvant therapy and is a necessary component of a comprehensive protocol. Education will promote patient compliance, give patients a sense of control, and improve treatment outcomes. Prior to the initiation of cancer treatment, patients should be instructed about possible side effects, including anemia and its related symptoms, especially fatigue. Providing patients with the appropriate knowledge to understand diagnosis and treatment enables them to become active partners in the plan of care and equips them to recognize any physical or lifestyle changes over time and notify the healthcare team for immediate intervention. Fatigue is the cardinal symptom of anemia (Gillespie, 2002), and oncology nurses play a pivotal role in educating patients about self-care skills to minimize the negative effects of fatigue on daily activities and quality of life (Mock, 2001; Ream & Richardson, 1999; Stovall & Young, 2006). Fatigue management includes identifying personal limitations, conserving energy, planning ahead for the efficient use of energy, alternating rest and activity periods, keeping regular sleep schedules, and exercising safely within capabilities (Portenoy & Itri, 1999). Education regarding nutrition is important to combat fatigue and vitamin deficiencies. If iron supplementation is required, patients should be advised regarding appropriate medication requirements (e.g., bowel regimen to prevent constipation). Integrating stress management techniques and cognitive therapies can minimize the impact of symptoms related to fatigue (Portenoy & Itri). Personal treatment diaries can provide subjective assessments on activity levels and actual nutrition and hydration intake, in addition to giving patients a sense of control and the means to identify changes over time.

Conclusion

Oncology nurses play a central role in risk assessment, symptom evaluation, evidence-based interventions, and determination of treatment options for their patients with CRA, making a significant contribution to improving patients’ quality of life and positively influencing clinical outcomes. Anemia traditionally has been a symptom that rarely was assessed carefully, perceived as producing little or no change in cancer outcomes (Gillespie, 2005). With the advent of erythropoiesis-stimulating therapies and the recognition of the debilitating impact of fatigue, the symptom clusters caused by CRA can no longer be ignored. Implementation of standards of care, essential laboratory studies, necessary iron and folate supplementation, pertinent documentation, and clinical monitoring of patient status have been widely inconsistent (Berger, 2005). Oncology nurses are in a key position to rectify clinical discrepancies and contribute to the research that is needed to determine the most effective interventions for patients (Berger). The impact of erythropoietic therapy on treatment response and survival outcomes and the role of prophylactic treatment with these agents still must be determined. Clinical management of anemia requires a comprehensive and holistic approach (Loney & Chernocky, 2000) across all patient care settings—goals inherent in the role of oncology nurses.

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