Anemia occurs frequently in veterinary cancer patients and may result from increased blood loss, decreased red blood cell (RBC) production (e.g., abnormal bone marrow function), or increased RBC destruction (e.g., immune-mediated diseases). More specific causes of malignancy-associated anemia include anemia of chronic disease, bone marrow invasion by tumor cells, marrow suppression by chemotherapy, hypersplenism, megaloblastic anemia, vitamin and iron deficiency, microangiopathic hemolytic anemia, and pure red cell aplasia. Anemia of any cause arising as an indirect effect of the tumor is a paraneoplastic syndrome. In most patients, a clear cause of anemia is not found and a diagnosis of “anemia of chronic disease” is made.

Blood loss anemia is seen in many types of cancer. It can be a direct effect of the cancer or an indirect result of coagulopathies linked with hemangiosarcomas, thyroid carcinomas, and inflammatory mammary carcinomas. Histamine released from mast cell tumors may activate parietal cells in the stomach, increasing production of hydrochloric acid and inducing gastric or duodenal ulceration and consequent blood loss. If anemia is secondary to blood loss, the cause may be obvious (as with bleeding superficial tumors) or inconspicuous (as with bladder or gastrointestinal tumors).

Microangiopathic hemolytic anemia is commonly seen in dogs with splenic hemangiosarcoma and occurs secondary to hemolysis because of damage to arteriolar endothelium or fibrin deposition within the artery. Disseminated intravascular coagulation (DIC) is an important cause of this type of anemia. Although hemangiosarcoma is the most common cause of DIC, a variety of other neoplastic diseases, such as thyroid carcinoma and inflammatory mammary adenocarcinoma, may result in anemia caused by DIC.

In dogs, immune-mediated hemolytic anemia (premature destruction of RBCs by immune mechanisms) is sometimes triggered by tumors (e.g., lymphoma). Antibodies can be directed against the RBCs or against a hapten (e.g., virus, drug) that is associated with the RBCs.

Chemotherapy-induced nonregenerative anemia is common in dogs. The condition is frequently associated with chronic drug therapy. Although chemotherapeutic agents often decrease the number of white blood cells (WBCs) and platelets, anemia associated with administration of chemotherapeutic agents generally is mild and is not associated with clinical signs. Hydroxyurea may cause anemia as its primary hematologic toxicity.

Less common causes of cancer-induced anemia include leukoerythroblastic anemia, hematopoietic dysplasia, hypersplenism, erythropagocytosis, megaloblastic anemia, and red cell aplasia.

**DIAGNOSTIC CRITERIA**

**Clinical Presentation**

Many of the mechanisms previously described work alone or in concert to decrease the population of RBCs. Although clinical signs relating to the anemia may be overshadowed by aspects of the underlying neoplastic condition, the anemia can nevertheless impair the quality of life of the animal. Most patients remain asymptomatic if anemia develops gradually or if the number of RBCs is only slightly decreased. As the anemia progresses, lethargy and exercise intolerance may arise. Mucous membranes may be pale.

**Diagnosis**

The anemia must first be classified as regenerative or nonregenerative. If the anemia is regenerative and serum proteins are decreased, blood loss may be considered. If serum proteins are increased, differentials of RBC destruction by immune-mediated diseases (e.g., immune-mediated hemolytic anemia), physical trauma (e.g., DIC, parasites), or toxins must be considered. If the anemia is nonregenerative, a bone marrow aspiration or biopsy should be performed to evaluate for erythroid hypoplasia (causes include anemia of chronic disease, endocrine deficiencies, renal disease, and lead toxicity), aplastic anemia (causes include estrogen toxicity and phenylbutazone), myeloproliferative disorders, and iron deficiency.

Anemia of chronic disease in cancer patients is associated with a shortened erythrocyte life span, depressed bone marrow response, and disordered iron metabolism and storage. Clinically, anemia of chronic disease is rec-

ognized as normocytic and normochromic, with normal bone marrow cellularity and reticuloendothelial iron sequestration. Blood loss anemia is recognized clinically when the RBCs are microcytic and hypochromic because of decreased hemoglobin synthesis. Poikilocytosis, microleptocytosis, inadequate reticulocytosis, increased total iron-binding capacity, decreased serum iron concentrations, and elevated platelet counts may also be seen with blood loss. Hemolysis and schistocytosis are the hallmarks of microangiopathic hemolytic anemia. The diagnosis of immune-mediated hemolytic anemia is based on finding antibody or complement on the surface of the patient’s RBCs by a Coombs’ test or slide agglutination test and scherocytes, paired with nonregenerative anemia. Histologically, chemotherapy-induced changes include bone marrow hypoplasia of the erythroid or other cell lines that subsequently causes inadequate reticulocytes and decreased RBC mass with normal erythrocytic indexes.

**TREATMENT RECOMMENDATIONS**

As with all paraneoplastic syndromes, the best treatment is eliminating the underlying cancer. Symptomatic treatment is usually needed only if the anemia produces clinical signs or if the animal is to undergo surgery. If acute correction of the condition is warranted, it is common to administer RBCs after a cross-match. Preparations of RBCs are listed in Table 1.

The following general guidelines for transfusion should be followed:

\[
\text{ml} = \left(\frac{(PCV_{\text{desired}} - PCV_{\text{recipient}})}{PCV_{\text{donor}}} \right) \times \left(2.2 \times \frac{\text{wt}_{\text{kg}}}{(40)}\right)
\]

**General Rule: Amount to Transfuse:**

NOTE: 2.2 ml of whole blood/kg or 1 ml/kg of packed RBCs raises the packed cell volume (PCV) 1% (transfused whole blood has a PCV of 40%).

**General Rule: Rate of Transfusion:** 0.5 ml/kg/hr or faster (22 ml/kg/day) with close patient monitoring.

Transfusion-associated graft-versus-host disease is a risk for all patients, not just bone marrow transplant recipients. Some advanced centers therefore recommend irradiating blood with 2.5 Gy before transfusion. Transfusion is of great help for many patients; however, it also carries the risk of transmitting infectious diseases. Peripheral progenitor cells are the latest development in hematologic supportive care associated with chemotherapy, but more work is needed before they are used to treat anemia on a routine basis in veterinary medicine.

Canine recombinant erythropoietin will soon be available; however, until it is, human recombinant erythropoietin (75–100 U/kg/day SC for 3–5 days, then three times a week; decrease to once or twice weekly when the desired hematocrit level is reached) is being used more commonly for a variety of anemias. Because recombinant erythropoietin is somewhat species specific, patients may develop antibodies to the recombinant protein, which may cross with the patient’s own erythropoietin. Recombinant erythropoietin is most effective when endogenous erythropoietin levels are low and when adequate erythrocyte precursors are present in the bone marrow and other structures. If anemia is attributable to blood loss, the source of bleeding should be identified and eliminated. Medical management of immune-mediated hemolytic anemia can include prednisone (2 mg/kg PO daily); in addition, azathioprine (2 mg/kg PO daily for 4 days, then 0.5–1.0 mg/kg PO every other day) may be indicated if resolution of the underlying neoplastic condition is delayed. Cyclosporine (5 mg/kg PO bid; dose adjusted by monitoring blood levels) is sometimes effective. Contrary to early reports, cyclophosphamide is probably of limited value in treating immune-mediated hemolytic anemia and associated conditions in dogs.

**RECOMMENDED READING**


