

ONCOLOGY

How to Approach Canine Leukemias in General Practice

Ali Hatamkhani, DVM, DVSc

University of Saskatchewan Western College of Veterinary Medicine, Saskatoon, Saskatchewan, Canada

Joanne Intile, DVM, MS, DACVIM (Oncology)

North Carolina State University College of Veterinary Medicine, Raleigh, North Carolina



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Abstract

Canine leukemias are a heterogeneous group of hematopoietic neoplasms that vary widely in presentation, progression, and prognosis. They may be discovered incidentally on routine bloodwork or present as life-threatening acute disease with severe cytopenias. Correctly distinguishing between acute and chronic leukemias, as well as differentiating between neoplastic and reactive causes of leukocytosis, is essential for guiding diagnostics, treatment, and effective client communication. Advances in diagnostic testing have improved classification, but practical interpretation and decision making remain vital skills in general practice. This article aims to familiarize general practitioners with the spectrum of canine leukemias, explain the rationale behind commonly used diagnostic tests, and provide a framework for helping clients make informed decisions about management options.

Take-Home Points

- Canine leukemias vary widely in behavior, prognosis, and treatment. Accurate diagnosis is essential for appropriate management.
- Acute leukemias are aggressive, rapidly progressive diseases characterized by large, immature cells and concurrent cytopenias. Patients are often clinically ill, and treatment involves intensive multiagent chemotherapy.
- Chronic lymphocytic leukemia (CLL) is typically slow to progress and often detected incidentally. Treatment is not required until specific criteria are met.
- Cytologic evaluation of a blood smear by a clinical pathologist is the recommended first step, but flow cytometry is the diagnostic gold standard and should be performed when possible.
- Clear client communication is crucial. CLL is usually manageable long-term, whereas acute leukemias carry a grave prognosis despite treatment.

Canine leukemias are common findings in general practice, whether as an acute, life-threatening condition in a patient presenting with cytopenias, anemia, or bleeding diathesis, or as an incidental finding on routine preoperative blood analysis. Often, the presentation holds the key to prognosis and treatment options.

The term “leukemia” encompasses a broad group of neoplasms of hematopoietic cells arising in the bone marrow (or sometimes spleen) that typically manifest as an otherwise unexplained increase in circulating white blood cells.¹ Leukemias in dogs range from indolent diseases requiring no immediate therapy to aggressive malignancies with rapid progression and short survival times despite treatment.

Advances in diagnostics, particularly flow cytometry, have enhanced the ability to classify leukemias; however, interpreting these results can be challenging. This article provides a practical approach for clinicians to diagnose, differentiate, and manage leukemias in a general practice setting, including treatment strategies, monitoring guidelines, and effective communication with clients regarding prognosis and management options.

Understanding Canine Leukemias: “Good” Versus “Bad”

Leukemias are broadly classified by cell maturity as acute or chronic and by cell lineage (lymphoid versus myeloid),² resulting in 4 categories:

- Acute lymphoid leukemia (ALL)
- Acute myeloid leukemia (AML)
- Chronic lymphocytic leukemia (CLL)
- Chronic myeloid leukemia (CML)

The distinction between acute and chronic leukemia is important, as each carries different prognoses and treatment approaches. Acute leukemias are “bad” in that they are aggressive diseases with short survival times. In contrast, chronic leukemias are often considered the “good” forms, as they tend to be slowly progressive and are associated with longer survival times (**TABLE 1**).

The most common leukemia in dogs is CLL, an indolent proliferation of small, mature lymphocytes. CML and other myeloproliferative disorders are exceedingly rare by comparison and are not discussed in detail in this article.

Acute leukemias are aggressive malignancies characterized by the presence of large, immature cells in the blood and bone marrow. These diseases carry a poor prognosis, and differentiation between subtypes such as ALL, AML, acute undifferentiated leukemia,

TABLE 1 Features of Acute and Chronic Leukemias

FEATURE	ACUTE LEUKEMIA	CHRONIC LEUKEMIA
Appearance of the cell/maturity	Immature/blast	Mature/differentiated
Presence of clinical signs	Common, usually sick	Uncommon, incidental
Speed of progression	Rapid	Slow
Ease of classification based on morphology	Difficult	Easier
Prognosis	Poor to grave	Good/often indolent
Treatment	Injectable chemotherapy	Oral chemotherapy; delay treatment as long as possible

and mixed-phenotype acute leukemia can be challenging due to cellular immaturity and aberrant expression of surface markers. Given the current limited treatment options and similarly poor outcomes across subtypes, they are discussed collectively in this article under the umbrella of acute leukemia.

Diagnosis

Step 1: Evaluate the Patient

The first step in approaching a suspected leukemia is to assess the patient's history and clinical presentation.

Chronic Lymphocytic Leukemia

CLL is frequently diagnosed incidentally, and the patient is often clinically healthy with no reported abnormal clinical signs and a normal physical examination. Some dogs have mild peripheral lymphadenopathy or palpable splenomegaly. If a chronic leukemia progresses, clinical signs develop, ranging from mild lethargy to more severe signs similar to those seen in dogs with acute leukemias.

CLL mostly occurs in older, small-breed dogs (median age, 10 to 11 years) with no sex predilection.¹ A classic scenario is when an otherwise healthy geriatric dog undergoes routine laboratory tests for an unrelated issue or anesthesia and is found to have an elevated lymphocyte count with no clinical abnormalities.

English bulldogs, a notable exception among larger-breed dogs, tend to develop CLL at a younger age (median age, 6 years).³ Additionally, the syndrome of persistent lymphocytosis, often accompanied by splenomegaly, has been described in this breed.³ This phenomenon indicates a non-neoplastic, polyclonal expansion of B cells rather than true CLL, and these

conditions can be distinguished by PCR for antigen receptor rearrangement (PARR) testing.^{3,4}

Hyperglobulinemia is present in approximately 25% of CLL cases, with a notably higher prevalence in English bulldogs (about 50% of cases).^{3,5}

Acute Leukemia

Dogs with acute leukemia usually show vague systemic signs such as lethargy, pyrexia, anorexia, or gastrointestinal signs; more specific physical examination findings include organomegaly (spleen larger than liver) and lymphadenopathy. Affected dogs can show signs of myelophthisis, manifesting as petechiae, pale mucous membranes, epistaxis, and other signs of spontaneous bleeding. It is rare to incidentally diagnose acute leukemia in an otherwise healthy dog.

Patients with acute leukemias are usually middle-aged (7 to 8 years), although disease can occur at any age. There is no sex predilection.⁶ The progression of the disease is usually rapid. If lymphadenopathy presents, it is usually less pronounced than in cases of high-grade multicentric lymphoma.

Step 2: Evaluate the Slides

The most valuable diagnostic test in cases of suspected leukemia is a CBC with blood smear examination by a clinical pathologist. The leukocyte count and differential reveal the magnitude of leukocytosis and the types of cells involved. In suspected leukemia, examination of a well-made blood smear is invaluable, as cell morphology can help establish a tentative diagnosis; however, for definitive diagnosis, more advanced diagnostics, including flow cytometry and cytochemistry with routine imaging tests, are required. In-house automated hematology analyzers might fail

to detect neoplastic cells and can misclassify them (e.g., identifying acute leukemia as CLL).⁷

In addition to identifying neoplastic cells, the CBC reveals any concurrent cytopenias. In CLL, the remainder of the CBC is often normal at diagnosis aside from the lymphocytosis. Mild anemia is present in some dogs with CLL, but severe cytopenias are uncommon. Acute leukemias commonly cause anemia (usually nonregenerative) and thrombocytopenia due to overcrowding of the bone marrow.

In rare instances, leukemia cannot be diagnosed solely by evaluating peripheral blood. Neoplastic cells might be confined to the bone marrow with no circulating neoplastic cells (aleukemic leukemia) or be present in low numbers despite a normal or decreased white blood cell count (subleukemic leukemia). This lack of neoplastic cells occurs more commonly, though not exclusively, in AML, making bone marrow evaluation essential for diagnosis in some cases.¹

Chronic Lymphocytic Leukemia

In CLL, the neoplastic cells are often morphologically indistinguishable from normal mature lymphocytes. They are typically small, with nuclei smaller than those of neutrophils, and contain dense, clumped chromatin and minimal cytoplasm. As a result, a blood smear in

CLL may appear relatively unremarkable, aside from a marked increase in the number of small lymphocytes.

Acute Leukemia

“If the cells are big, it’s bad.” In acute leukemia, the circulating neoplastic cells are predominantly immature and are larger than normal neutrophils (the nucleus is larger than that of a neutrophil). Some clinical pathologists describe them as “big blue cells.”⁸ These cells typically have fine to reticulated chromatin, 1 or more visible nucleoli, and a high nuclear-to-cytoplasm ratio with basophilic cytoplasm.

Lymphoblasts and myeloblasts have a similar large, immature appearance, making it challenging to distinguish between them based on cytologic features alone. Nevertheless, the presence of a significant population of large, immature, hematopoietic cells in the blood should raise immediate concern for acute leukemia or stage V lymphoma. Mitotic figures might occasionally be observed on the smear in acute leukemia due to the high rate of cell proliferation.

Is This Leukemia?

An important initial step in diagnosing leukemia is to differentiate true leukemias from non-neoplastic causes of extreme leukocytosis. The 2 common white blood cell types that are responsible for leukocytosis are neutrophils and lymphocytes.

Neutrophilic leukocytosis in dogs is far more often reactive (e.g., severe infection or inflammation causing a leukemoid reaction) than neoplastic; true chronic neutrophilic leukemia is exceedingly rare. Thus, an unexplained extreme mature neutrophilic leukocytosis (segmented neutrophils $\geq 50 \times 10^3$ cells/ μ L) should prompt a thorough search for underlying infection, inflammation, or marrow stimulation before leukemia is considered as a diagnosis.^{9,10} Neutrophilic leukocytosis can also be a paraneoplastic syndrome secondary to a cancer other than leukemia, such as carcinoma, intestinal lymphoma, metastatic fibrosarcoma, and even rectal polyps.¹

Lymphocytic leukocytosis can occur secondary to antigenic stimulation (e.g., *Ehrlichia canis* infection) or Addison’s disease, but such reactive lymphocytoses are usually mild to moderate in magnitude. Persistent lymphocyte counts above 20 000 to 30 000/ μ L are uncommon in chronic infections and raise concern for lymphoproliferative neoplasia.

GLOSSARY

- **Acute leukemia** Leukemia comprising immature, undifferentiated cells
- **Clonality** All cells derived from a single original cell, as in neoplasia
- **CHOP** A chemotherapy protocol comprising cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and prednisone.
- **Chronic leukemia** Leukemia comprising mature, well-differentiated cells
- **Myelophthisis** Cancer cells crowding out the bone marrow
- **Stage V lymphoma** Lymphoma with bone marrow involvement and neoplastic cells circulating in the peripheral blood. Note that involvement of any tissue beyond the lymph nodes, liver, or spleen is classified as stage V lymphoma.

As mentioned, English bulldogs can present with a unique syndrome of non-neoplastic small B-cell lymphocytosis that mimics CLL. Although the degree of lymphocytosis (median, ~22 000/ μ L) is typically less marked than in true CLL, the clinical presentation is similar.³

Most non-neoplastic causes of persistent lymphocytosis in dogs are rare, and most dogs with sustained, marked small-cell lymphocytosis have CLL or stage V indolent lymphoma.² In practice, a high lymphocyte count that is repeatable and unexplained by other diseases should prompt diagnostic evaluation for leukemia or lymphoproliferative disease.

Step 3: Establish a Definitive Diagnosis

Flow Cytometry

Cellular morphology aids in the diagnosis of leukemias; however, for a definitive diagnosis, flow cytometry is the preferred diagnostic tool (**BOX 1**). Flow cytometry evaluates cells by their size (forward scatter) and granularity (side scatter) and can detect various cell surface (or intracellular) markers to identify the cell type. It is worth noting that flow cytometry does not directly determine clonality; instead, clonality can only

BOX 1

When Morphology and Flow Cytometry Results Don't Match

Morphology and flow cytometry results can yield discordant results. For example, some cases show large cells on blood smear yet are diagnosed as chronic lymphocytic leukemia (CLL) by flow cytometry. In contrast, other leukemias, particularly acute leukemias, might exhibit coexpression of both T-cell and B-cell markers. In such instances, clinical signs and disease progression should be carefully considered. While flow cytometry is regarded as the gold standard for diagnosis, it is essential to inform owners that some cases diagnosed as CLL might behave more aggressively and progress rapidly, resembling acute leukemia in their clinical course.

be inferred from flow cytometry results. Definitive determination of clonality is achieved with PARR. Cellular markers are used to differentiate various types of leukemia (**BOX 2**).¹¹⁻¹³

Sample Handling

Flow cytometry requires live cells; therefore, proper sample collection and handling are critical. Viability is usually assessed early in the analysis using stains such as propidium iodide, as data from dead cells can be misleading. Most laboratories reject samples with more than 50% nonviable cells. Blood or bone marrow should be collected in EDTA and ideally arrive at the laboratory for processing within 24 to 48 hours. Samples should be refrigerated (not frozen) and shipped early in the week to avoid delays. Results are accompanied by an interpretive summary from the clinical pathologist, which can be very helpful in understanding the diagnosis.^{11,12}

Chronic Lymphocytic Leukemia

Canine CLL is typically classified into 2 major immunophenotypic subtypes: T-cell CLL (T-CLL), which accounts for approximately 75% of cases, and B-cell CLL (B-CLL), which makes up the remaining 25%.² This distribution contrasts with human CLL, which is almost exclusively of B-cell origin. Among canine T-CLLs, most are CD8⁺, and many exhibit large granular lymphocyte morphology. CD4⁺ T-CLL is rare. Canine B-CLL is characterized by the expansion of CD21⁺ B cells. Unlike human B-CLL, which frequently shows aberrant expression of the T-cell marker CD5, canine B-CLL typically lacks CD5 expression.¹⁴

BOX 2

Common Cellular Markers in Leukemia

- CD3 (T lymphocytes)
- CD4 (helper T cells)
- CD8 (cytotoxic T cells)
- CD34 (progenitor cells)
- CD79a (B lymphocytes)
- MHC class II (leukocytes)

CD = cluster of differentiation; MHC = major histocompatibility complex

Acute Leukemia

Most acute leukemias express CD34, a cell surface antigen that is expressed on early hematopoietic progenitor cells and lost as cells mature. Its expression on neoplastic cells has been associated with a poor prognosis.¹⁵ Some ALLs are CD34-negative; therefore, the absence of CD34 does not exclude a diagnosis of acute leukemia if other diagnostic features are supportive. Additionally, some dogs with lymphoma have neoplastic lymphocytes that aberrantly express CD34.^{1,11,16,17}

Flow cytometry is essential for subclassifying acute leukemias. Neoplastic cells expressing lymphoid markers are categorized as ALL, while those expressing myeloid markers are considered AML. In some cases, neoplastic cells lack definitive lineage markers, consistent with acute undifferentiated leukemia, or coexpress markers from multiple lineages, consistent with mixed-phenotype acute leukemia.¹⁸ Despite these distinctions, all subtypes carry a poor prognosis, and in many primary care settings, the differentiation might not substantially affect immediate management. However, distinguishing between AML and ALL might be clinically relevant, as treatment strategies differ. ALL in dogs is almost exclusively of T-cell origin, and some believe that true B-cell ALL is rarely, if ever, encountered in this species.^{15,19}

Immunocytochemistry/Cytochemistry

Immunocytochemistry (ICC) or cytochemistry (CC) is the application of specific dyes or antibodies to cytology preparations, analogous to immunohistochemistry on histopathology samples. The key difference is that CC uses chemical dyes that react with general cellular components (e.g., alkaline phosphatase staining in suspected canine AML) while ICC employs antibodies to detect specific antigens (e.g., CD3 or CD79a to distinguish canine ALL subtypes).¹⁷ These techniques highlight targets on or within cells, aiding in classification. ICC/CC can be performed on unstained or previously stained cytology slides. It is not widely available; however, some specialty diagnostic laboratories offer it as an add-on to cytology.

Historically, ICC/CC was the only tool for distinguishing AML from ALL in dogs. Today, it has largely been supplanted by flow cytometry, which provides more comprehensive immunophenotyping. Still, ICC/CC remains valuable, either as a complement

to flow cytometry or when fresh samples suitable for flow cytometry are unavailable.

PARR

PARR detects clonality and is primarily used to distinguish neoplastic from non-neoplastic conditions. For example, PARR can help differentiate the polyclonal lymphocytosis seen in English bulldogs from true CLL.³ Unlike flow cytometry, PARR does not require viable cells. It can be performed on a variety of tissues, including stained cytology slides sent for clinical pathologist evaluation, making it an attractive option. However, it is not recommended for immunophenotyping, as results might be misleading. Neoplastic cells may exhibit clonality across multiple lineages, complicating interpretation. In addition, more than half of AML cases might have aberrant PARR-positive results, which could lead to misclassification as ALL.¹⁶

Differentiating Acute Leukemia Versus Stage V Lymphoma

Distinguishing between acute lymphoblastic leukemia and stage V high-grade lymphoma can be diagnostically challenging. Both conditions can present with elevated counts of large immature lymphocytes in circulation. No single test definitively differentiates acute leukemia from stage V lymphoma. Flow cytometry can be helpful, and the expression of CD34 supports a diagnosis of acute leukemia. However, not all cases of acute leukemia express CD34. Lymphadenopathy is generally less pronounced than in patients with lymphoma, while the total white blood cell count tends to be markedly higher in leukemia. However, exceptions can occur.

A mediastinal mass can be detected in both lymphomas and acute leukemias. Its presence does not favor a diagnosis of lymphoma over leukemia—nearly half of dogs with AML present with a mediastinal mass.¹⁸ This distinction does not significantly impact initial management, but it can influence the prognosis. Both ALL and stage V high-grade lymphoma are treated with multiagent injectable chemotherapy protocols (e.g., CHOP). Dogs with stage V lymphoma (especially B cell) sometimes respond to chemotherapy and achieve remissions measured in months, whereas acute leukemia often responds transiently, and the disease progresses rapidly.

CASE EXAMPLE 1**Chronic Lymphocytic Leukemia in a Maltese****History and Presentation**

Martha, a 12-year-old spayed female Maltese, was presented to her primary care veterinarian for a dental procedure. On physical examination, she had severe gingivitis, dental tartar, and halitosis. Mildly enlarged mandibular lymph nodes were detected, which were initially attributed to her dental disease. No organomegaly was detected on abdominal palpation, and rectal examination was unremarkable.

Routine preanesthetic blood analysis revealed lymphocytosis (9546 cells/ μ L). No other CBC abnormalities were noted. Serum biochemistry and urinalysis were unremarkable. An in-house blood smear revealed small, mature lymphocytes. The dental procedure was postponed pending clarification of the lymphocytosis.

Diagnosis and Treatment

A blood sample was sent to a clinical pathologist, who confirmed mature lymphocytosis and recommended further evaluation with flow cytometry (**FIGURE A**). A fresh EDTA blood sample was collected and shipped on ice. Flow cytometry documented a CD8+ T-cell lymphocytosis, consistent with chronic lymphocytic leukemia (CLL).

Since Martha was otherwise clinically unremarkable and the lymphocytosis was not severe, no treatment was initiated. She subsequently underwent her dental procedure uneventfully.

Six months after initial presentation, Martha's CBC showed leukocytosis (57030/ μ L) characterized by lymphocytosis (48120/ μ L). Physical examination was unremarkable. Recheck in 2 months was advised.

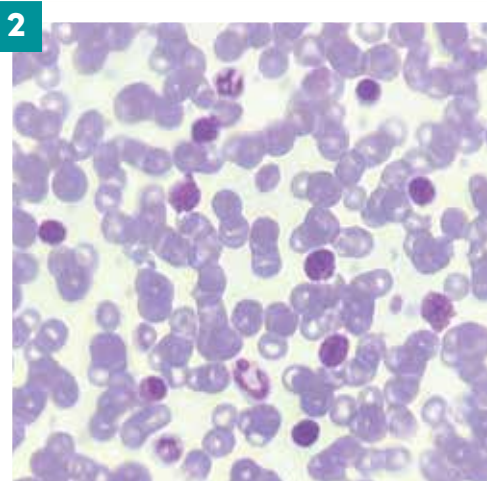
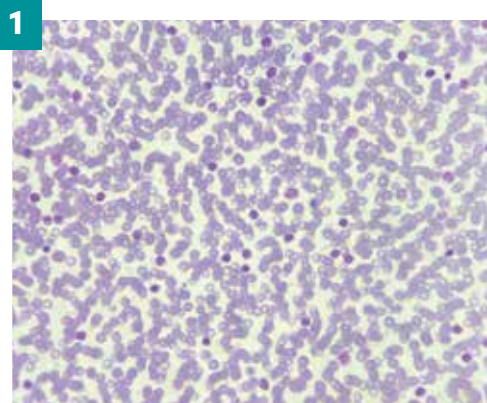


FIGURE A. Blood smear from Martha demonstrating predominantly small, mature lymphocytes consistent with chronic lymphocytic leukemia. **(1)** 10 $\times$ objective. **(2)** 100 $\times$ objective. Wright-Giemsa stain.

TABLE A Martha's Serial CBC Changes Over Time*

Date	01/31/22	07/20/22	09/25/22	10/19/22	11/02/22	12/05/22	01/02/23
Hematocrit	39.9%	35.5%	32.9%	28.4%	32.5%	35.1%	32.0%
Platelets	348 000	578 000	351 000	354 000	539 000	537 000	469 000
White blood cells	12 900	57 030	111 360	74 700	27 900	29 100	27 600
Neutrophils	3225	6910	6040	9170	10 602	8439	10 764
Bands	0	suspected	suspected	suspected	558		
Lymphocytes	9546	48 120	101 310	61 410	16 182	19 497	14 904
Monocytes	129	1690	3760	3940	837	873	1380
Eosinophils							

*Treatment started 10/5/2022

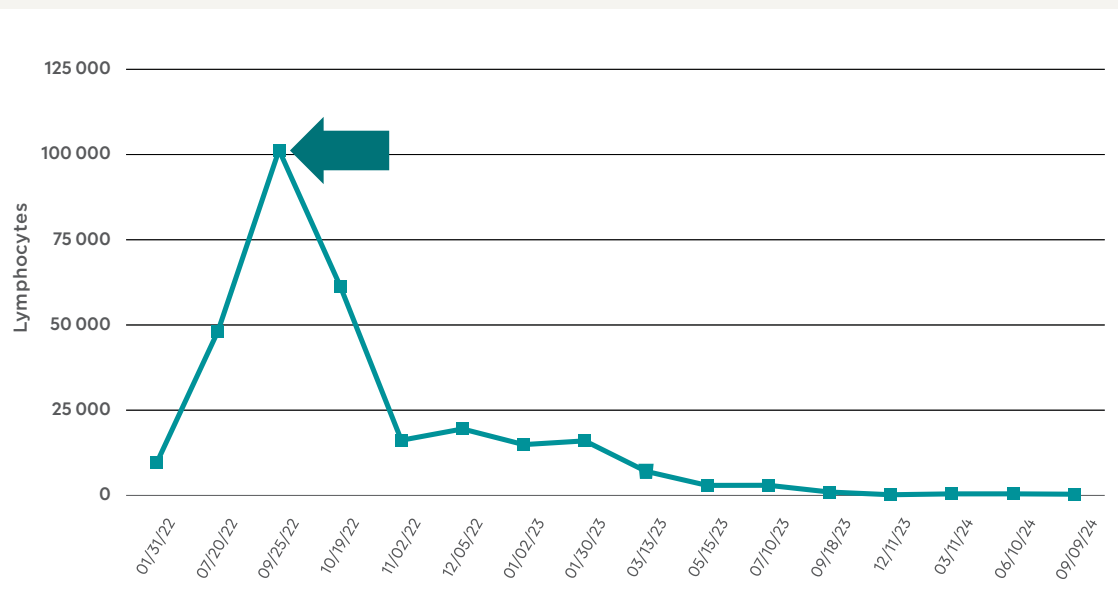


FIGURE B. Treatment was initiated 8 months after diagnosis (arrow), once marked leukocytosis and clinical signs developed.

Eight months after initial presentation, a CBC revealed progression of leukocytosis (111360/ μ L) with lymphocytosis (101310/ μ L). Mild peripheral lymphadenomegaly was present. Martha also developed a rectal prolapse after an episode of diarrhea, attributed to sublumbar lymphadenomegaly, and was less energetic according to the owner.

At this point, treatment with prednisone (1 mg/kg PO q24h) and chlorambucil (6 mg/m² PO q48h) was initiated. Prednisone was tapered to 0.5 mg/kg PO q24h after 1 week.

One month after starting therapy, Martha's CBC showed marked improvement, and peripheral lymphadenomegaly had resolved (**TABLE A AND FIGURE B**).

Follow-up

Over time, the recheck interval was extended to every 2 months, then every 3 months. Martha maintained an excellent quality of life and remained in complete remission.

Two years and 10 months after her initial diagnosis, Martha was euthanized after being hit by a car. At that time, she remained in complete remission from CLL.

01/30/23	03/13/23	05/15/23	07/10/23	09/18/23	12/11/23	03/11/24	06/10/24	09/09/24
34.1%	32.7%	32.8%	36.9%	36.0%	36.0%	39.1%	38.6%	36.7%
559 000	588 000	390 000	484 000	513 000	550 000	542 000	623 000	593 000
25 000	21 400	16 100	12 900	14 170	9 740	11 290	11 410	17 430
7 250	11 984	13 989	8 643	11 619	8 474	9 597	10 155	13 944
0	0	173	258	0	97	0	0	174
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Managing Chronic Lymphocytic Leukemia

When to Treat Versus When to Monitor

The first decision to be made in managing dogs with CLL is whether to initiate treatment. Generally accepted indications to begin treatment include:

- The patient develops clinical signs attributable to CLL (e.g., lethargy, poor appetite, unexplained weight loss).
- There is evidence of bone marrow compromise (e.g., moderate to severe anemia not due to other causes, thrombocytopenia developing as the lymphocyte count rises).
- Significant organomegaly is present (e.g., enlarged spleen or liver causing discomfort, markedly enlarged lymph nodes).
- The lymphocyte count is excessively high (commonly a threshold of around 30 000 to 60 000/ μ L is used) or rising rapidly over successive rechecks.

If any of these criteria are met, treatment should be initiated. If none are present, a conservative approach is appropriate, including monthly physical examinations and CBCs, or every 2 to 3 months in stable cases. It is essential to educate clients that CLL is typically a slow-progressing disease and that immediate treatment is not required unless clinical signs are present. This helps prevent overtreatment and avoids exposing dogs to unnecessary adverse effects.

Treatment Protocol

If treatment is warranted, the most commonly used and well-tolerated protocol for canine CLL is a combination of chlorambucil and prednisone. The authors use the following treatment protocol:

- **Chlorambucil:** 6 to 8 mg/ m^2 PO q48h or 20 mg/ m^2 every 2 weeks. For long-term maintenance, a lower dose (e.g., 2 mg/ m^2 q48h) can be used, with adjustments made based on clinical response and bone marrow tolerance.
- **Prednisone:** Administered concurrently at an initial immunosuppressive dose of 1 mg/kg q24h for 1 to 2 weeks, then tapered to 0.5 mg/kg q48h.

Most dogs show a favorable response within a few weeks to months, with declining lymphocyte counts

and a reduction in lymphadenopathy or splenomegaly. Approximately 70% to 80% of dogs achieve a partial or complete remission with this combination.¹⁴ There is no consensus on the optimal duration of treatment. The authors typically continue therapy for up to 2 years; however, this remains an area of debate, and some oncologists elect to stop treatment about 1 year after remission while some continue treatment indefinitely. In nonresponders, vincristine can be added or cyclophosphamide substituted for chlorambucil.

Monitoring

Unlike more intensive chemotherapy protocols, chlorambucil at these doses rarely causes significant myelosuppression. However, mild neutropenia or thrombocytopenia occasionally occurs; therefore, periodic monitoring of CBCs is recommended. Prednisone-related adverse effects, such as polyuria, polydipsia, and polyphagia, are common, particularly during the initial stages of treatment, but are generally manageable for most owners, especially as the dose is tapered over time.

At the authors' institutions, follow-up for dogs with CLL begins with baseline diagnostics before initiating treatment, including a CBC, serum biochemistry profile, and urinalysis. After starting therapy, CBC and body weight are monitored every 2 weeks for the first month. If the patient remains stable, monitoring continues monthly until 6 months after treatment initiation. At this point, both a CBC and biochemistry panel are repeated. If the patient remains in remission, CBC and body weight checks are extended to every 2 months for 1 year after starting treatment. A complete reevaluation, including CBC, biochemistry, and urinalysis, is then performed.

If remission is maintained, follow-up can occur every 3 months for the first year and then every 6 months for the second year. In select cases where remission persists 2 years after starting therapy, the authors consider discontinuation of chlorambucil, tapering of prednisone, and continued monitoring every 3 months. See **CASE EXAMPLE 1** for a real-world case report of CLL.

Managing Acute Leukemias

Initial Stabilization

Dogs with acute leukemia often present in hematologic crisis and require stabilization even before a definitive diagnosis. Severe anemia or thrombocytopenia should be addressed with transfusions as needed to stabilize the patient. Aggressive intravenous fluids are indicated if tumor lysis is a concern or the patient is dehydrated.

Chemotherapy

Once acute leukemia is diagnosed and the necessary samples are obtained, prompt initiation of multiagent chemotherapy is the primary treatment approach. Many oncologists initiate treatment with a CHOP-based multiagent chemotherapy protocol comprising cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and prednisone, similar to the approach used for high-grade lymphoma. Some oncologists prefer to modify the order of drugs in the first treatment cycle by administering doxorubicin earlier, giving it after the initial vincristine dose and delaying cyclophosphamide, or by adding L-asparaginase in an effort to achieve remission more rapidly. However, there is no evidence that these modifications improve overall outcomes. If the diagnosis of AML is confirmed, a combination of doxorubicin and cytarabine is used every 2 weeks for 6 doses of each, either both administered on the same day or in an alternating weekly schedule.²⁰

One notable phenomenon during induction is the risk of acute tumor lysis syndrome (ATLS). If the circulating blast count is extremely high, the rapid killing of tumor cells by chemotherapy can release large amounts of intracellular contents—potassium, phosphorus, and nucleic acids—into the bloodstream. This can lead to life-threatening metabolic disturbances such as hyperkalemia; hyperphosphatemia with secondary hypocalcemia; and, in some cases, acute kidney injury. However, although ATLS is well-documented in human leukemias, it is rare in dogs.²¹ While uric acid contributes significantly to renal damage in humans, most dogs convert uric acid to the more soluble allantoin through hepatic uricase, making hyperuricemia less clinically significant, except in predisposed breeds such as the Dalmatian and the English bulldog. Hospitalization for 24 to 48 hours post-treatment to provide intravenous fluids, monitor

electrolytes, and initiate prophylactic treatments if needed may mitigate the risk of ATLS.^{21,22}

See **CASE EXAMPLE 2** for a real-world case report of acute leukemia.

Prognosis and Client Communication

Managing owner expectations is essential when discussing a diagnosis of leukemia, as the term can be understandably alarming. Many clients might relate it to human cases, which vary widely in prognosis and might involve treatments such as bone marrow transplants, options that are typically not available or appropriate in veterinary medicine. It is essential to have a clear and compassionate discussion that outlines the treatment goals, potential costs, and realistic expectations for outcomes.

Chronic Lymphocytic Leukemia

Conversations with owners of dogs diagnosed with CLL should address prognosis, the monitoring plan, and long-term management. Owners should be informed that CLL is typically a slow-progressing, manageable disease. In many cases, immediate treatment is not necessary, and early intervention does not improve survival in humans.²³ Many dogs with CLL live comfortably for extended periods and might ultimately die of unrelated causes, especially since most are older and might have other comorbidities.

Boxers with CLL have significantly shorter median survival times (approximately 6 months) compared with other breeds. This poorer outcome might be explained by the high prevalence of unmutated immunoglobulin heavy chain variable region (*IGHV*) genes in boxers (about 80% of boxers with CLL versus roughly 25% of nonboxers). The presence of an unmutated *IGHV* gene is a well-recognized negative prognostic factor in human CLL.^{14,24}

A clear plan for regular monitoring and defined criteria for initiating treatment should be outlined as mentioned above. When therapy is indicated, most dogs tolerate chlorambucil and prednisone well at home, with periodic rechecks to monitor response. Providing an expected survival range (e.g., 1 to 3 years) offers hopeful but realistic expectations. While

CASE EXAMPLE 2**Acute Leukemia in a Nova Scotia duck tolling retriever****History and Presentation**

A 9-year-old intact male Nova Scotia duck tolling retriever, Tucker, was presented for lethargy and inappetence of 1 week's duration. The owner reported that he was too weak to walk unassisted.

On physical examination, Tucker was quiet but alert and responsive. His heart rate was mildly elevated, and mucous membranes were pale pink with a capillary refill time of 2 seconds. Cardiothoracic auscultation revealed a grade I/VI systolic heart murmur without arrhythmias or abnormal lung sounds. Abdominal palpation revealed marked splenomegaly, and the prescapular and popliteal lymph nodes were mildly enlarged. Rectal examination confirmed melena. The remainder of the examination was unremarkable.

Diagnosis and Treatment

A CBC showed marked leukocytosis ($456 \times 10^3/\mu\text{L}$) with 76% ($346 \times 10^3/\mu\text{L}$) large immature cells (**FIGURE A**). Severe nonregenerative anemia (hematocrit [HCT] 12%) and marked thrombocytopenia (estimated platelet count $50\text{--}75 \times 10^3/\mu\text{L}$) were also present (**FIGURE B**). These findings were consistent with acute leukemia and secondary myelophthisis.

The poor prognosis and need for hospitalization to initiate therapy were discussed with the owner, who elected to proceed with treatment. Tucker was hospitalized and transfused with packed red blood cells. Chemotherapy was initiated with vincristine ($0.7 \text{ mg}/\text{m}^2 \text{ IV}$) and dexamethasone ($0.1 \text{ mg}/\text{kg} \text{ IV}$). Because of the marked leukocytosis and concern for acute tumor lysis syndrome, intravenous fluids were initiated and continuous electrocardiographic monitoring was provided.

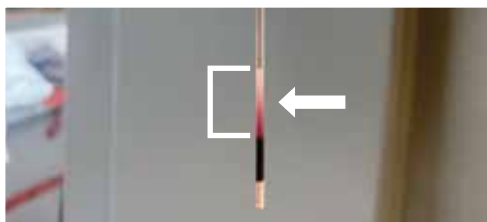


FIGURE B. Microhematocrit from Tucker. Neoplastic cells extensively infiltrated the bone marrow, resulting in myelophthisis and reduced production of other hematopoietic cell lines. Note the disproportionately thick buffy coat (**arrow**), representing markedly increased white blood cells, compared to the thin buffy coat in a normal microhematocrit.

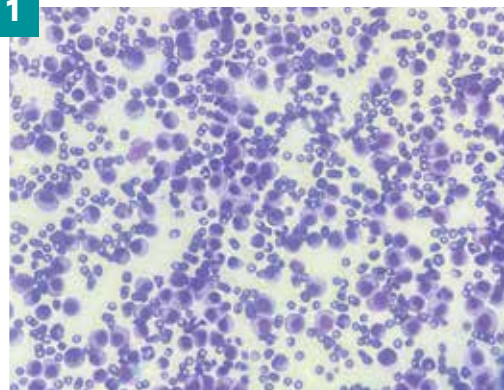
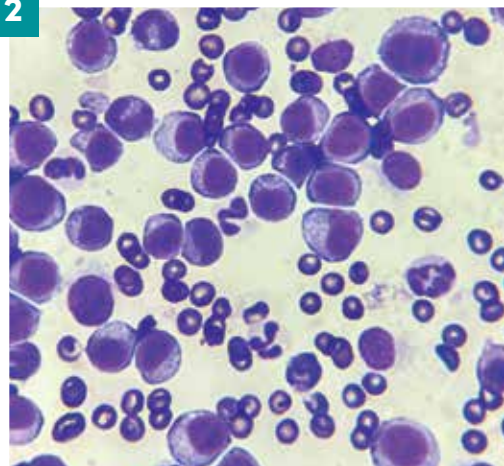
1**2**

FIGURE A. Blood smear from Tucker. Note the large size of neoplastic cells in comparison to neutrophils and red blood cells. **(1)** 10× objective. **(2)** 100× objective. Diff-Quik stain.

During hospitalization, Tucker's demeanor, energy, and appetite improved significantly. He was discharged 48 hours later. A repeat CBC before discharge still showed marked leukocytosis ($203.2 \times 10^3/\mu\text{L}$) with 63% neoplastic cells ($128 \times 10^3/\mu\text{L}$) and persistent thrombocytopenia (platelets $\sim 10 \times 10^3/\mu\text{L}$) but improved anemia (HCT 21%). He was prescribed prednisone ($1 \text{ mg}/\text{kg} \text{ PO q24h}$) and supportive medications for nausea and appetite stimulation.

Outcome

Tucker returned for weekly chemotherapy. Although partial remission was achieved and there was significant clinical improvement, the leukemia ultimately progressed. He was euthanized 2.5 months after the initial diagnosis.

prolonged survival is common, CLL is considered incurable. About 5% of CLL cases progress to a highly aggressive lymphoma known as Richter's syndrome or Richter's transformation, typically occurring late in the course of the disease. This transformation is characterized by marked peripheral lymphadenopathy and the presence of large lymphocytes, distinct from those seen in the original CLL. Regardless of treatment, Richter's syndrome carries a poor prognosis, with a median survival of only 41 days.^{25,26}

Acute Leukemia

For acute leukemia cases, the primary focus is on maintaining quality of life while setting realistic expectations. Owners must understand that acute leukemias carry a grave prognosis. Even with intensive multiagent chemotherapy, the goal, similar to that with many other cancers, is for the patient to feel better on treatment than off. Responses are often rapid; however, relapses are common and typically occur quickly. Median survival time with palliative treatment (prednisone only) is about 7 days. Median survival times with chemotherapy are approximately 2 months, although some patients might experience longer benefits.⁶

Summary

Inevitably, general practitioners will encounter leukemia cases in clinical practice, whether acute or chronic. Understanding the differences in behavior, prognosis, and treatment options among the various types of leukemia, as well as the interpretation of diagnostic tests, empowers practitioners to effectively inform clients and provide optimal patient care. **TVP**

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CE Quiz Questions

1. Which of the following statements is an accurate prognosis for acute lymphoid leukemia (ALL) treated with multiagent chemotherapy?
 - a. Median survival is roughly 12 months for B-cell leukemia and 6 months for T-cell leukemia.
 - b. Prednisone alone yields a median survival of 2 to 3 months.
 - c. Median survival is about 2 months; responses can be short-lived.
 - d. Survival mirrors that seen with stage V lymphoma.
2. Acute tumor lysis syndrome in dogs with very high circulating blasts is:
 - a. Common and driven primarily by uric acid in most dogs
 - b. Rare; consider 24- to 48-hour hospitalization with IV fluids and electrolyte monitoring after induction.
 - c. Prevented by using corticosteroids
 - d. Not associated with electrocardiographic changes
3. PARR is most useful to:
 - a. Decide between ALL and acute myeloid leukemia (AML)
 - b. Quantify marrow blast percentage
 - c. Predict response to chlorambucil
 - d. Confirm clonality when distinguishing bulldog polyclonal lymphocytosis from chronic lymphocytic leukemia (CLL)
4. Richter's transformation in canine CLL is characterized by which of the following?
 - a. Transformation to indolent T-zone lymphoma with long survival
 - b. Rapid transformation to aggressive large-cell lymphoma with poor prognosis
 - c. Switch from B-cell to T-cell CLL with reduced survival
 - d. Development of paraneoplastic hypercalcemia
5. Which finding alone is not a standard indication to begin treatment in a dog with CLL?
 - a. Rising lymphocyte count above ~60,000/μL
 - b. Moderate thrombocytopenia
 - c. Splenomegaly and lethargy
 - d. Lymphocyte count of 20,000/μL in an asymptomatic dog

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Authors



Ali Hatamkhani

Dr. Hatamkhani completed his DVM degree at Azad University–Karaj in Iran, followed by a residency in small animal internal medicine at the University of Tehran, Iran. He spent a year visiting the medical oncology service at North Carolina State University, then returned to Iran and established the country's first veterinary oncology service at Nikan Pet Hospital in Tehran. Following 6 years of oncology practice, he moved to Canada. He later completed a rotating internship at the Atlantic Veterinary College, University of Prince Edward Island. He is currently a medical oncology resident at the Western College of Veterinary Medicine, University of Saskatchewan.



Joanne Intile

Dr. Intile completed her DVM degree at Cornell University and her rotating internship in small animal medicine and surgery at Long Island Veterinary Specialists. She returned to Cornell for her residency in medical oncology and then worked in private specialty practices in New York and Maryland. Dr. Intile's time spent as an adjunct instructor in the veterinary science technology program at Suffolk County Community College solidified her career goal of working in academia. She joined the faculty of the North Carolina State University College of Veterinary Medicine in 2017.