MANAGING FELINE GI LYMPHOMA IN PRACTICE 2024

Sue Ettinger, DVM, DACVIM (Oncology)
Dr Sue Cancer Vet PLLC
Sleepy Hollow, NY, USA

Lymphoma (LSA) is one of the most commonly occurring cancers in cats. Lymphoma is a systemic disease that requires chemotherapy in almost all cases. Treated cats live longer, and chemotherapy is generally well-tolerated. Unlike dogs, outcomes including response rates and survival times for treated cats are less predictable, but cats tend to tolerate chemotherapy better than dogs. The most common form of lymphoma in cats is gastrointestinal lymphoma. Gastrointestinal lymphoma can be divided into large cell/high grade and low grade/small cell forms. This is also referred to enteropathy-associated T-cell LSA (EATL) type I. This talk will focus on the intermediate to high-grade gastrointestinal form of feline lymphoma, but we will also discuss the small cell/low-grade form.

WHAT IS IT:
Lymphoma is one of the most common feline cancers, reported at 30% of all cancers. It is a systemic disease that requires chemotherapy in almost all cases. It is a collection of cancers arising from the malignant transformation of lymphocytes. In contrast to dogs, feline lymphoma most commonly affects the gastrointestinal (GI) tract. Lymphoma can occur in cats of any age, any sex, any breed. The GI form typically occurs in middle aged cats of 10 to 11 years old. The small intestines are four times more affected than the large intestines. Intermediate to high-grade form of feline lymphoma is also referred to enteropathy-associated T-cell (EATL) lymphoma type I. This is a large cell lymphoblastic lymphoma. This form often has a palpable abdominal mass. This contrasts with EATL Type II, which is the small cell, low grade, lymphocytic lymphoma. This form is more diffuse throughout the gastrointestinal tract, and the history is usually chronic over several months, with a median of 6 months.

WHAT I SAY TO OWNERS:
Gastrointestinal lymphoma is a treatable cancer but outcomes for treated cats are less predictable than dogs. The cats that receive treatment with a multi-agent protocol and those that achieve a complete remission tend to be the ones longer survival times. Cats tend to tolerate chemotherapy better than dogs. Treated cats live longer, and chemotherapy is generally well-tolerated. I would and have treated my own cat.

CLINICAL APPEARANCE:
Clinical signs include weight loss due to malassimilation, vomiting, diarrhea, hyporexia to anorexia, and less commonly icterus. The onset is more rapid than cats with low grade lymphoma, and it typically occurs over days to weeks. A palpable abdominal mass is common. Hepatosplenomegaly may be present. Physical examination may also be normal. Rarely the cat will present with acute abdomen due to obstruction or perforation. Alimentary lymphoma typically involved the intestines alone or intestines, abdominal lymph nodes (LN), and liver. In the GI tract, it can be solitary or diffuse.

For low grade small cell lymphoma, clinical signs include weight loss due to malassimilation (83-100%), vomiting/diarrhea (73-88%), anorexia (66%), and icterus (7%). 70% have abnormal palpation on exam, either thickened GI or a palpable mass 33%. The history is usually chronic over several months, with a median of 6 months. The cats typically have a poor body condition and ill-kempt appearance.

RISK FACTORS & ETIOLOGY
Viral: In the FeLV era from the 1960-1980s, lymphoma accounted for 50-90% of hematopoietic tumors. FeLV-positive cats had a 62-fold increased risk. This form was predominantly seen in younger cats, was the mediastinal form, T-cell, and the virus had a direct role in tumorigenesis. Being FIV-positive increased lymphoma incidence by 5-6x. In contrast to FeLV, FIV has an indirect role secondary to immunosuppressive effects and is associated with B-cell and the extranodal form. Cats that are both FeLV and FIV positive have an increased risk of 77-fold. However, there was a shift after the 1990s, also called the post FeLV-era. With the aid of FeLV diagnostic assays and elimination regimens in 1970s and 1980s, there was a dramatic decline in FeLV-associated LSA. Still lymphoma prevalence is increasing, especially the alimentary form.
Immunosuppression: FIV has an indirect role with lymphoma secondary to immunosuppressive effects. Ten percent of feline renal transplants develop lymphoma following transplant and associated immunosuppressive therapy.
Environmental: Environmental tobacco smoke (ETS) has been reported to increase the risk of lymphoma by 2.5 to 3.2-fold.
Genetic and molecular factors: The predisposition of oriental breeds suggests a heritable risk, but this is still being investigated.

Chronic inflammation: While definitive proof is lacking, there is growing evidence of the link with chronic inflammation and lymphoma, with and intestinal lymphoma. This has been as area of interest with IBD and GI lymphoma.
Diet and GI lymphoma: While definitive proof is lacking, the diet changes over last 20 years in response to diseases such as urinary tract and the increase in GI lymphoma has led to the suggestion of a link, but more studies are needed.

DIAGNOSTICS:
Early accurate diagnostics and careful staging are keys to proper clinical decision-making. The diagnosis is typically straightforward for high grade lymphoma, and the diagnosis is typically made with abdominal ultrasound and cytology of a lymph node or organ. Surgery is less commonly needed. Cytology may be inconclusive and be reported as benign hyperplastic and reactive, and histology will be needed, but this is less common than cases of small cell/low grade lymphoma. In addition, the minimum tests required for chemotherapy treatment are CBC, chemistry panel and urinalysis. For the GI forms, 23% have panhypoproteinemia and 76% are anemic. I also recommend testing for FeLV/FIV status since FeLV-positive is a negative prognostic factor. Serum cobalamin/folate levels should be evaluated; hypocobalaminemia is associated with high- and low-grade lymphoma but is also seen with inflammatory bowel disease (IBD).

Additional tests to consider include thoracic radiographs, lymph node histology, bone marrow cytology and phenotyping. Bone marrow cytology may be recommended especially for cases with anemia, leukopenia, or cellular atypia. Phenotype can be determined with PARR (about 80% sensitive) or flow cytometry. Currently, I only recommend PARR testing if histopathology was inconclusive as phenotype is not prognostic in cats (which is different from dogs). While all these staging tests are useful and informative, as they provide prognostic factors and a baseline for a patient's response, we must consider the owner's financial issues. I consider each test on a case-by-case basis and help the owner make an educated decision. I recommend choosing the more important tests for that cat based on presentation, physical exam and diagnostic findings, and the owner's budget.

To confirm the diagnosis of **low-grade lymphoma**, histopathology is typically needed. Cytology is rarely useful for distinguishing low-grade GI LSA vs IBD. Unlike high grade lymphoma, cytology may be inconclusive and be reported as benign hyperplastic and reactive, and histology will be needed, and in some cases and may require phenotyping and clonality testing. The debate rages on regarding endoscopy vs full thickness biopsy (laparotomy vs laparoscopy). While endoscopy is less invasive, the samples are not full thickness and cannot reliably reach portions of the intestines like the jejunum. On histopathology, LSA typically has lymphoid infiltration beyond the mucosal layer, epitheliotrophism, heterogeneity, and lymphocyte nuclear size consistent with malignancy. If the diagnosis is still equivocal, phenotyping with PARR testing (about 80% sensitive) is recommended. Currently, we only recommend PARR testing if histopathology was inconclusive as phenotype is not prognostic in cats (which is different from dogs.)

Prognostic factors: The prognosis and response rates to chemotherapy in cats with lymphoma are more variable than in canine lymphoma. Prognostic factors include anatomic location, achieving a complete remission, FeLV-status, substage, and a multi-agent protocol (CHOP vs COP protocols). Factors that are NOT prognostic in cats include stage and immunophenotype, age, weight, gender, and FIV status. Remember, prognostic factors cannot predict an individual's response, and lymphoma is typically treatable and rewarding to treat for the patient, owner, and the veterinarian.

TREATMENT:
Dogs vs Cats
There are fewer feline data than for canine lymphoma. Papers often lump together small number of cases of multiple subtypes of various anatomic, phenotype and histologic grades. Outcomes are less predictable in cats, and there is greater variation in histologic type and anatomic location in cats. But cats tolerate chemotherapy well and better than dogs. Febrile neutropenia is rare in cats. Most owners happy they chose to treat, and the quality of life improves, and clinical signs resolve or improve.

Chemotherapy for high grade lymphoma:
Improved remission rates and durations are achieved with combination chemotherapy protocols, and there are numerous protocols reported in the literature. There is an overall response of 50-80%, a median remission of 4 months, and median survival times (MST) of 5 to 9 months. Cats that achieve a complete remission have a longer median survival time of approximately 1 year. I typically recommend a **CHOP multi-agent** protocol such as the UW 25-week protocol. When using doxorubicin in cats, I use a lower dose (1 mg/kg IV). Cardiac toxicity is not clinical problem in cats in contrast to dogs, and renal function (BUN, Cr, USG) should be monitored in cats when giving doxorubicin. In dogs, data supports shorter maintenance-free protocol, but there is less data in cats, and some cats may need chronic maintenance chemotherapy.

An alternative protocol is the **COP protocol** with reported complete remissions of 50-70%. This is commonly used in used in Europe with similar results to CHOP in 1 study. While the protocol requires less frequent visits, it is a longer 1-year protocol. Other studies support the addition of doxorubicin to COP for durable responses.

For single agent options, oral **Lomustine** can be given at 50-60 mg/m^2 every 4-6 weeks, which is given at a lower dose and less frequently than dogs. While complete response rates were low at 22%, some cats experienced a remission rate of 10 months. Single agent doxorubicin is cats is less successful with complete remission rates of about 26% and a median of 3 months, and I do not recommend this as a single agent (unlike dogs). I also recommend supplementing cobalamin as indicated.

Other treatments: Chemotherapy remains the standard therapy as lymphoma is a systemic disease. A recent report in cats with discrete high grade GI lymphoma treated with **surgical resection** followed with CHOP chemotherapy had a median survival time of 12 months. **Whole-abdominal radiation therapy** after abbreviated induction chemotherapy may improve outcome.

If chemotherapy is declined: If chemotherapy is declined, another option is single agent steroids. I prefer prednisolone in cats and recommend treatment if clinical response is seen. Typical response rates are 50% with duration of 2 to 3 months. Without chemotherapy the prognosis for lymphoma is poor, with MST of about 1 month.

Chemotherapy for low grade lymphoma:

For low grade lymphoma, less aggressive oral chemotherapy protocols are typically used than cats with high grade LSA. Oral chlorambucil (Leukeran®) can be dose with pulse dosing (20mg/m^2 every 2 weeks or 15 mg/m^2 for 4 days every 3 weeks) or with chronic dose (>4 kg start @ 2 mg PO q 2 days, maintenance q 3 days; <4 kg start @2 mg PO q 3 days, maintenance q 4 days). I typically do the chronic dose protocol. For cats, oral prednisolone is preferred, typically at 1 - 2 mg/kg daily, reducing to 0.5 to 1 mg/kg daily. In some cases, prednisolone may eventually be discontinued. Chlorambucil can cause delayed myelosuppression specifically neutropenia and thrombocytopenia, and liver toxicity. Routine monitoring of CBC and chemistry panels is recommended.

For relapsed cases, cyclophosphamide, Lomustine, and vinblastine are recommended. Lomustine can be given at 50-60 mg/m2 every 4-6 weeks, which is given at a lower dose and less frequently than dogs. For severe or refractory cases, CHOP or COP multi-agent protocols can be used, similar to treating intermediate and high-grade lymphoma.

Nutrition for low grade/small cell lymphoma: With evidence of role of inflammation and many have concurrent IBD, there is thought to consider transition to a novel protein diet and to add probiotics. I also recommend serum cobalamin levels and supplementing as indicated.

Chemotherapy side effects and GI lymphoma in cats:

Chemotherapy is well tolerated in most dogs and cats undergoing treatment. The overall toxicity rate is very low in veterinary chemotherapy patients. In my experience, only 15-20% experience side effects, and this is even less common in cats than dogs. The primary goal is to provide the best quality of life possible for as long as possible. As I say**, live longer, live well.** Most side effects are mild and medically manageable.

Gastrointestinal (GI) toxicity secondary to chemotherapy includes vomiting, diarrhea, decreased appetite, nausea. These are the same clinical signs that the GI lymphoma causes. Chemotherapy side effects typically occur 1 to 5 days after chemotherapy and are self-limiting – lasting on average 2 to 3 days. Even those side effects are less common in feline chemotherapy patients than in dogs, **I recommend being very proactive with nausea/anti-emetic drugs in cats with feline GI lymphoma since they often present with clinical signs similar to the potential side effects from chemotherapy**.

As in people, a common and dreaded side effect of chemotherapy treatment is Chemotherapy-Induced Nausea and Vomiting (CINV). As with other causes of inappetence it is important to be proactive, not reactive, especially in cats with GI cancer. Most of these cats have vomiting, diarrhea, weight loss, and some degree of inappetence PRIOR to chemotherapy. Concurrent medical conditions can also contribute and exacerbate CINV, such as pre-existing renal disease, renal disease, pain, and medications such as antibiotics. Additional preventative medications are recommended in these patients.

JUST IN CASE MEDICATIONS AND INFORMATION SHEET

I recommend all patients go home on the first day of chemotherapy with Cerenia, Mirataz, metronidazole, a probiotic, and the client information sheet. My client information sheet that walks owners through managing side effects at home can be found at on my website in the Resources section. (https://drsuecancervet.com/pet-owner-resources/). Similarly, patients that present with inappetence or have diseases associated with inappetence should also go home with medications (Mirataz®, Elura®) and guidelines. I also have videos and resources on my YouTube channel to help owners as well.

PROGNOSIS FOR HIGH GRADE LYMPHOMA:

Without Treatment: Approximately 1 month

With treatment: Improved remission rates and durations are achieved with combination chemotherapy protocols. Multi-agent CHOP protocols are typically the most successful. For high grade GI lymphoma, response rates are 50-75%, median remission duration is 4-6 months, and expected survival is 6 to 9 months. However, cats that achieve completer remission can be long term survivors, and 15-25% can live 1 to 2 years. With steroids only, typical response duration is 2 to 3 months.

PROGNOSIS FOR LOW GRADE LYMPHOMA:

In general, the prognosis for the low-grade GI lymphoma is associated with longer survival times than the high-grade forms. Remission is generally defined as improvement or resolution of clinical signs, and 70%-85% will respond for a median survival time of longer than 1 to 2 years.

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