WALTHAM® Feline Medicine Symposium 2003
in association with The North American Veterinary Conference

Therapeutic Choices for the Medical Management of Feline Lymphoma

Leslie E. Fox, DVM, MS, Diplomate ACVIM (Internal Medicine)
College of Veterinary Medicine, Iowa State University
Ames, IA, USA

INTRODUCTION

Changes in disease frequency and presentation of feline lymphoma necessitate a somewhat different approach to protocol selection and supportive care. The incidence, signalment, and etiology of this disease has changed during the 80's and 90's. Overall, it appears that feline leukemia virus infection has declined along with the frequency of some anatomic forms. Previously, lymphoma was most commonly a disease of younger, FeLV antigen positive cats often with mediastinal or multicentric involvement. Today, the younger cat with lymphoma is likely to be FeLV antigen positive, however, most affected cats are older (10–12 years old), FeLV antigen negative with the alimentary anatomic form predominating. Lymphoma involving the peripheral nodes and extranodal lymphomas are diagnosed more frequently as well. Compared with earlier studies, FIV is more common. An association between FIV- induced immunosuppression and lymphoma has been demonstrated in infected cats. Additionally, there are geographic differences in the causation and frequency of anatomic types of lymphoma as well as, differences in response to the same protocols based on geography.

Recent changes in the presentation of feline lymphoma make selecting and delivering potentially efficacious treatment that meets the needs of the individual patient challenging. In almost all cases, feline lymphoma is a systemic disease that needs to be treated systemically. With the exception of a subset of GI lymphomas, a multidrug protocol that includes at least doxorubicin and l-asparaginase, is the most efficacious, well-tolerated, treatment protocol currently available. Solitary lymphoma can be treated with surgery or radiation therapy followed by multidrug chemotherapy. Many cats (more than 85% in one study) are sick either from their lymphoma or because of unrelated geriatric diseases. Nutritional support is essential during the first 3–6 weeks of therapy for all patients, but particularly for those patients with gastrointestinal (GI) involvement. Geriatric patients often have age-associated diseases such as renal insufficiency, hyperthyroidism, and diabetes mellitus which complicate therapy and need be addressed before chemotherapy is initiated.

It is possible to predict the long-term outcome for many patients in the first 4–6 weeks of a multidrug chemotherapy protocol that includes doxorubicin and l-asparaginase, such as the AMC and UW-Madison-Wisconsin protocols (See Table 1). After 4–6 weeks of therapy, the patient will have received five of the most commonly used drugs with antitumor activity against lymphoma. At the end of 6 weeks, it is possible to make a good assessment of protocol efficacy and potential drug toxicity. The cat's initial response to therapy tells you, perhaps more reliably than any other factor, how the treatment is going to progress. While cats with a partial response to therapy (greater than 50% reduction in tumor size) often enjoy improved quality of life, cats with an initial complete response to therapy live longer (12–18 months vs 6–8 months). Generally, cats that have not responded favorably to the first 4–6 weeks of therapy continue to have a poor response to therapy despite the addition of other drugs. Likewise, cats that experience frequent adverse drug events requiring treatment delays and dose reductions often continue to have difficulty tolerating other anticancer drugs. Repeated dose reductions resulting in subtherapeutic treatment dosages will shorten disease free interval and decrease lifespan.

Table 1. Selected Protocols for the Treatment of Feline Lymphoma

- **Cotter-COP**
  - Day 1, 8, 15, 22: Vincristine 0.75 mg/m² IV
  - Day 1, 22: Cyclophosphamide 300 mg/m² PO
  - Every day: Prednisone 2 mg/kg PO
  - After day 22, vincristine and cyclophosphamide were given on the same day every 3 weeks until relapse or for one year if remission maintained. Also, Mahoney, Moore, Vail.
- **Moore-COP plus Doxorubicin: COP as above**
  - If complete remission is achieved, then begin doxorubicin, 25 mg/m², IV every 3 wks for 6 additional months
- **Jeglum-VCM**
  - Week 1 and 3: Vincristine 0.025 mg/kg IV
  - Week 2: Cyclophosphamide 10 mg/kg IV
  - Week 4: Methotrexate 0.8 mg/kg IV
  - Every day: 5 mg prednisone PO
  - Continue for 2 years. Mediastinal form–add l-asparaginase, 400 U/kg, IM on week 1.
- **Mooney-VCM plus l-asparaginase with high dose prednisone**
  - Week 1: l-asparaginase, 400 U/kg, IM
  - Week 1 and 3: Vincristine 0.025 mg/kg IV
  - Week 2: Cyclophosphamide 10 mg/kg IV
  - Week 4: Methotrexate 0.8 mg/kg IV
  - Every day: 2 mg/kg prednisone PO
  - Continue for 2 years
  - For renal lymphoma after complete remission substitute cytosine arabinoside 600 mg/m² SQ for cyclophosphamide.
- **Rassnick, Mauldin, Zwahlen-AMC Protocol (ACOPA-M)**
  - Week 1: l-asparaginase 400 IU/kg IM
  - Week 1, 4, 8 and 12: Vincristine 0.025 mg/kg IV
  - Week 2, 5, 10: Cyclophosphamide 10 mg/kg IV
  - Week 3, 6: Doxorubicin 20 mg/m² IV
  - Week 14: Methotrexate 0.8 mg/kg IV
  - Every day: prednisone 5 mg/cat PO BID
  - If in complete remission, biweekly maintenance therapy consisting of week 8, 10, 12 and 14 therapy is given for 12 months. If still in complete remission, then the same protocol is given triweekly for 6 months and then increased to 4-week intervals between treatments for 6 months. Therapy is given for a total of 2 years.
- **MacEwen-University of WI-Madison**
  - Week 1, 3, 8, 11, 12, 15, 19, 23: Vincristine 0.7 mg/m² IV
  - Week 1: l-asparaginase 400 IU/kg IM
  - Week 2, 7, 13, 21: Cyclophosphamide 250 mg/m² IV
  - Week 4, 9, 25: Doxorubicin 20 mg/m² IV
  - Week 17: Methotrexate 0.8 mg/kg IV
  - Every day for the first 2 weeks: Prednisone 2 mg/kg PO, then 1 mg/kg PO daily

- Continue protocol biweekly for weeks 11–25, then tri-weekly for 6 months, then monthly for 6 months. Therapy is given for 2 years total. Also, Vail.

- **Malik-modified AMC—See ref # 7**
- **Mauldin-MOPP**
  - Days 1 and 8: Mechlorethamine at 3.0 mg/m^2 IV and vincristine at 0.025 mg/kg IV
  - Days 1 through 14: Procarbazine at 10 mg PO once daily
  - Every day: 5 mg/cat PO BID
- **Rassnick-MOPP-AC**
  - Days 1 and 8: Mechlorethamine at 3.0 mg/m^2 IV and vincristine 0.5 mg/m^2 IV
  - Days 1 through 14: Procarbazine 10 mg/cat PO once daily
  - Every day: Prednisone 40 mg/m^2 PO daily
  - Days 22, 57, 99, 141, 183: Doxorubicin 25 mg/m^2 IV
  - Days 36, 78, 120, 162, 204: Cyclophosphamide, 200 mg/m^2 IV + vincristine 0.5 mg/m^2 IV
  - If in complete remission at week 30, protocol is discontinued.

REVIEW OF RESPONSE TO PROTOCOLS

Single agent chemotherapy has been tried with disappointing results. While mitoxantrone was not helpful in 10/11 cats, doxorubicin was associated with somewhat better responses, but was not very effective at inducing and maintaining remission. In one study, 5/19 (25%) had a complete remission; however, the median response duration was 3 months. Lomustine (CCNU) has been evaluated in a small number of cats where partial remissions were achieved. Idarubicin has been used with reasonable success for inducing and maintaining remission; however, currently it is available only in Europe.

The **multidrug COP protocol** consisting of cyclophosphamide, prednisone, and vincristine has been one of the standard protocols for feline lymphoma treatment; however, the reported response and survival rates vary with time and geography. In a 1996 study of 38 northeastern American cats, 18/38 (47%) had a complete remission lasting less than 3 months. The responders were 6/11 (54%) cats with multicentric lymphoma, 5/12 (41%) cats with alimentary lymphoma, and only 2/9 (22%) cats with renal lymphoma. In comparison, a 1983 study of 38 cats with features less typical than we see today (i.e., more cats were FeLV antigen positive and had mediastinal lymphoma), the complete remission rate was high (30/38 79% cats) and the median response duration was 5 months. Geographic differences may be responsible for the good response to COP therapy reported in 2002 study of cats living in the Netherlands. Most cats were FeLV antigen negative and mediastinal lymphoma was the most common form. Complete remission was achieved in 46/61 (75%) cats with an overall median remission duration of 8.3 months and median survival time of 8.8 months.

The **addition of doxorubicin and/or l-asparaginase** has improved remission and survival times in most studies. Moore, *et al*. used doxorubicin as maintenance therapy after complete remission was achieved with COP. Median remission duration for the 7 cats that received doxorubicin after COP was 9.3 months versus 2.6 months for cats treated with COP alone. Two cats were still in remission one and 1.5 years after starting COP/doxorubicin.

Jeglum, *et al*., used COP plus l-asparaginase and methotrexate to treat 75 cats with a 52% complete response with a median response duration of 5 months. Cats with multicentric lymphoma had the best response with a median survival time of 18 months. 9/32 (29%) in the study lived longer than 2 years. Mooney *et al*. treated 103 cats with a similar protocol (AMC) where 64/103 (62%) had a complete remission with a 7-month median survival time and 19/64 (29%) lived beyond 1 year. Using the same protocol, Mooney, *et al*. showed 17/28 (61%) cats with renal lymphoma achieved a complete response to combination therapy, but median survival times were

short (5.7 months). Mauldin *et al*. treated 132 cats with primarily GI lymphoma (72%) with most cats FeLV antigen negative and clinical substage b or sick with the AMC protocol. In that study, 67% achieved complete remission with a first remission duration for all 132 cats of 4.9 months (range, 1 day–5.4 years) and median survival time of 6.9 months (range, 0.5 month–5.6 years). More recently, Zwahlen, *et al*., treated twenty-one FeLV antigen negative cats with GI lymphomas with the AMC protocol and 8/21 (38%) had a complete response. Median first remission was 9.8 months and median survival time was 10.2 months.

Using a procarbazine, vincristine, prednisone, and mechlorethamine combination (MOPP) plus doxorubicin/cyclophosphamide of Rassnick and coworkers, 52% of cats had a CR with a median survival time of 6.5 months. Forty-two percent (15/35) of cats had multicentric and 12/35 (34%) cats had extranodal lymphomas. Some cats were long-lived (5 cats were still alive at 1.5–2 years after the initiation of therapy).

Second remissions are difficult to achieve and short-lived in cats. Information about effective protocols is scarce. If COP was used successfully to induce a first remission, then the addition of doxorubicin and/or l-asparaginase may help reinduce remission. If a doxorubicin/l-asparaginase protocol was used initially and complete remission was achieved, then the first 4 weeks of that effective protocol can be given again. The MOPP protocol can be used for rescue for cats with refractory lymphoma. In a Mauldin, *et al*. study, 17/27 (74%) had GI lymphoma and most were FeLV antigen and FIV antibody negative. The overall response rate was 13/23 (56%) with additional median remission duration of 3 weeks and median survival about 2 months after initiation of MOPP protocol. Although well tolerated, mechlorethamine is not currently available to veterinary patients. Ifosfamide (900 mg/m^2 every 3 weeks, IV) in conjunction with diuresis and mesna for patients without renal insufficiency may be helpful in the future.

Maintenance therapy for cats is needed until otherwise demonstrated. Cats treated with COP without any maintenance therapy by Cotter stayed in remission for a median time of 45 days. In contrast, dogs treated with a high dose, multidrug, doxorubicin-containing protocols given without maintenance therapy live as long as dogs treated with added maintenance therapy. Current investigations are underway to determine whether feline lymphoma behaves similarly.

Extranodal or solitary lymphoma can be treated with combined therapy consisting of surgery or radiation therapy and chemotherapy or with chemotherapy alone. If the tumor is easily resectable, then surgical excision is appropriate; however, resection of solitary GI masses has not improved survival. Lymphocytes are exquisitely sensitive to even low doses of radiation, so only a few treatments may be necessary to relieve thoracic or spinal compression with a response often observed only a few hours after a single dose. In a study of cats (Elmslie, *et al*.) with subcutaneous, nasal, oral, mediastinal, and retrobulbar lymphoma treated with 8–40 Gy, most cats achieved a complete remission which lasted 6 months to 5 years, but most cats received chemotherapy as well. Spinal lymphoma is may be best treated with combinations of surgical debulking, radiation therapy, and systemic chemotherapy; however, there are few reports of long-term survival.

Since it is impossible to identify the very few cats that might be cured with local therapy alone, cats with focal lymphoma are presumed to have systemic disease and should be treated with multidrug chemotherapy. Small number of cats with nasal lymphoma have been evaluated, but it appears that they enjoy the longest remission and survival times. It is unclear whether chemotherapy alone, focal radiation therapy, or combination therapy constitutes the best therapy. Confirmation of focal nasal lymphoma with careful clinical staging (including bone marrow aspiration cytology) may identify a subpopulation that responds favorably (>1.5 years MST) to radiation therapy alone; however, there is insufficient numbers of treated cats to recommend not treating for systemic disease at this time.

Table 2. Remission Rates, Times, and Survival Times for Cats Treated for Lymphoma

Author–Protocol	Tumor Location	Cases	Complete Remission Rate (%)	Median Remission (Mos)	Median Survival (Mos)	Reference
Cotter-COP	Thymic	12	92	6.0	NR	1
Mahony-COP	Alimentary	7	86	4.5	NR	6
Moore-COP	Peripheral nodes	5	80	2.8	NR	12
	Multicentric	4	100	5.0	NR	
	Overall	NR.	79	5.0	NR	
	Alimentary	28	33	7.0	1.5	
	All Anatomic Types	38	47	3.0	NR	
Moore-COP + Doxorubicin	All Anatomic Types	7	47	9.2	NR	12
Teske-COP	Mediastinal	22	82	8.3	8.7	15
	Miscellaneous	11	73	5.7	4.6	
	Alimentary	11	63	8.1	6.3	
	Nasal	8	75	11.9	*	
	Peripheral	7	85	12.6	20.8	
	Overall	61	75	8.3	8.8	
Jeglum-VCM + 1-asp	Thymic	31	45	2.0	2.6	4
	Alimentary	9	50	6.0	9.6	
	Renal	6	16	NR	5.0	
	Multicentric	16	68	NR	18.0	
	Overall	NR	52	NR	2.0	
Mooney-AMC	Renal	28	61	5.0	5.7	11
Mooney-AMC	All types	103	62	7.0	7.0	10
Rassnick-AMC	Alimentary	31	71 (PR+CR)	4	6.7 overall If CR, then 8.6	6
Malik–modified AMC	All types	61	80	If in CR, then 3.7	3.8 If in CR, then 6.2	7
Mauldin-AMC	All Anatomic Types	132	67	4.9	6.9	9
Zwahlen-AMC	Alimentary	21	38	10	10.3	18
MacEwen-UW-Madison	All types	22	68	9.1	7.5	17
Rassnick - MOPP-AC	All Anatomic Types	34	52	NR	6.5	13

NR = Not reported

* Median not reached

CR = complete remission

PR = partial remission

PROGNOSTIC VARIABLES AFFECTING RESPONSE TO THERAPY

Few prognostic factors are consistently associated with remission and survival. Although the cat's initial response to therapy is the most consistent variable influencing remission and survival times, histomorphology of GI lymphomas, tumor location, tumor burden (clinical stage) and the presence of systemic illness have been found to influence treatment outcome.

Histomorphology of gastrointestinal (GI) lymphoma may be used to guide treatment selection. GI lymphoma can be histologically graded into lymphocytic, intermediate, and lymphoblastic subtypes. Fondacaro, *et al*., treated 29 cats with lymphocytic lymphoma with a minimal protocol consisting of chlorambucil (15 mg/m^2 per day for 4 days, every 2 weeks) and prednisone (10 mg/cat/day). Twenty of twenty-six cats (76%) achieved a complete remission. Median remission duration for cats in complete remission was 20.5 months (5.8–49 months) with a median survival time of almost 2 years (10–50 months). Cats that came out of remission were treated with cyclophosphamide (225 mg/m^2 every 3 weeks, PO) with a 6-month increase in median survival time for responders. Eight cats with lymphoblastic lymphoma were treated with the AMC protocol and only 2/8 (21%) cats achieved a complete remission lasting 12 and 17 months.

Cats with nasal, peripheral nodal, in some reports, **mediastinal lymphoma** may live longest, while cats with renal, CNS, spinal lymphoma and nonacute lymphoblastic leukemias have shorter survival. In Klein and coworkers, 19 cats with nasal lymphoma were treated with chemotherapy alone, 6 with radiation therapy alone, and 8 with both chemotherapy and radiation therapy where median survival times were 5, 19.7, 5.9 months. Using COP alone, Teske, *et al*., treated 8 cats with nasal lymphoma where 6/8 cats (75%) achieved a complete remission lasting a median of 1 year. With COP, Cotter treated 5 cats with peripheral node involvement, 4/5 (80%) achieved complete remission with a median remission time of 28 months. There are no reports of median survival times greater than about 5 months for cats with renal lymphoma. The nervous system is either involved at the time of diagnosis or becomes affected soon after.

Cats that are FeLV antigen and FIV antibody negative and have **Clinical Stage I or II** live longest. Cats with advanced clinical stage (Clinical Stage III, IV, and V) do not live as long as cats with less extensive disease (Clinical Stage I and II) (about 2 months median survival time vs 7.5 months). Cats with a large tumor burden, thus advanced clinical stage are less likely to go into remission. Cats with massive abdominal tumor volume or severe hepato/splenomegaly are not as likely to achieve a complete remission when compared with cats with less tumor burden (50% vs 90%). It appears that in every protocol evaluation, a subset of cats enjoys long-term survival of 1.5 to 3 + years regardless of anatomic type or clinical stage. It is not known what distinguishes these cats from other shorter-lived patients.

The sick cat with lymphoma is perhaps the biggest challenge to achieving a good response to therapy. Cats that are sick at the time of diagnosis are more likely to experience adverse events associated with anticancer drugs and do not survive as long as cats who are otherwise "healthy." Using a modified AMC protocol, 20 Australian cats that survived at least 16 weeks after the start of therapy had a median survival time of 2.3+ years. The FeLV antigen or FIV antibody positive cat can be treated with the same multidrug protocols administered at the same dosages/frequency as unaffected cats. In all but one study, FeLV infected cats were as likely to have a complete response to therapy as noninfected cats, but as might be expected, they do not live as long because of complications from cytopenias and infectious disease.

IMPROVING YOUR RESULTS AND CLIENT SATISFACTION

Human patients who receive **adequate nutrition** live longer and experience fewer adverse drug effects than malnourished patients. With appropriate supportive care, most cats enjoy a good quality of life during therapy. Loss of appetite is the most common adverse effect. Megestrol acetate (2.5–5 mg/cat PO once a day) or cyproheptadine (1–4 mg/cat PO once a day) may stimulate appetite. Supplemental feeding is imperative for cats with GI lymphoma. Since appetite stimulants are not practical for long-term maintenance of feline patients, nasogastric, pharyngostomy, or gastrostomy tube feeding is strongly recommended for inappetant and/or underweight cats. Extensive upper GI disease may necessitate jejunal feeding. Most cats need between 200 and 300 Kcal/day that require 6 to 9 oz of a complete and balanced, canned cat food (1–1.5 kcal/ml). If the cat responds to chemotherapy, then tube feeding is usually needed for 3–6 weeks.

Vomiting is reported with varying frequency among protocols, but little is said about the frequency of antiemetic therapy for these patients. Metoclopramide (0.2–0.4 mg/kg PO q 8 hours) is an effective antiemetic for most patients with chemotherapy-induced vomiting. We give metoclopramide before giving cyclophosphamide, doxorubicin, vincristine, mechlorethamine and methotrexate routinely and send 2 days of medication for administration by owners. Withholding food the morning of therapy is advisable. Additional, affordable antiemetics include chlorpromazine (0.2–0.4 mg/kg SQ q 8h) and prochlorperazine (0.1–0.5 mg/kg IM or SQ q 8 hr).

Anxiety is a problem for some cats receiving weekly chemotherapy. We first try giving valium at home or soon after arrival at the clinic. If that doesn't decrease anxiety, then hydromorphone (0.05–0.1 mg/kg IM) combined with butorphanol (0.05–0.1 mg/kg IM) is given. Acepromazine (0.01–0.05 mg/kg IM) may be added if needed. Placement of a vascular access port at the start of therapy makes drug administration almost effortless. (Access Technologies, Norfolk Veterinary Products, Skokie, Il, 60076) Blood samples are easily obtained and drugs may be given via the same port. When not in use, catheter patency is maintained with a heparinized saline flush every 4–5 weeks.

Renal insufficiency is the most common cause of adverse drug effects in elderly human patients with cancer. With adequate hydration, supportive care (erythropoietin, transfusions) and judicious drug dosing, cats with chronic renal failure can be successfully treated and have a fair prognosis. Doxorubicin and cyclophosphamide should be used with caution. Procarbazine, piroxicam, and methotrexate should be avoided in cats with renal insufficiency. Drugs with little renal excretion such as vincristine, vinblastine, l-asparaginase, chlorambucil, lomustine, and prednisone may be used with reasonable safety. Cats requiring frequent IV fluid support as well as IV chemotherapy, benefit greatly from permanent vascular access port placement.

REFERENCES

1. Cotter SM. Treatment of lymphoma and leukemia with cyclophosphamide, vincristine, and prednisone, II: Treatment of cats. J Am Anim Hosp Assoc 19:166-172, 1983.
2. Elmslie RE, et al. Radiotherapy with and without chemotherapy for localized lymphoma in 10 cats. Vet Radiol 32;277-280, 1991.
3. Fondacaro JV, et al. Feline gastrointestinal lymphoma: 67 cases (1988-1996). Eur J Comp Gastroenterol 4:5-11, 1999.
4. Jeglum KA, et al. Chemotherapy of lymphoma in 75 cats. J Am Vet Med Assoc 190:174-178, 1987.
5. Klein MK, et al. Feline nasal lymphoma: A retrospective analysis Proceedings 15th Annual Conference of the Veterinary Cancer Society, 79-80, 1995.
6. Mahony OM, et al. Alimentary lymphoma in cats: 28 cases (1988-1993) J Am Vet Med Assoc 207:1593-1598, 1995.
7. Malik R, et al. Therapy for Australian cats with lymphosarcoma. Aust Vet J 79:808-818, 2001.
8. Mauldin GE, et al. MOPP chemotherapy as rescue for cats with refractory lymphoma, Proceedings from the 19th Annual Veterinary Cancer Society Meeting, p 98, 1997.

9. Mauldin GE, Chemotherapy in 132 cats with lymphoma: 1988-1994, Proceedings from the 15th Annual Veterinary Cancer Society Meeting, page 35-36, 1995.
10. Mooney SC, et al. Treatment and prognostic factors in lymphoma in cats: 103 cases (1977-1981). J Am Vet Med Assoc 194:696-699, 1989.
11. Mooney SC, et al. Renal lymphoma in cats: 28 cases (1977-1984) J Am Vet Med Assoc 191:1473-1477, 1987.
12. Moore AS, et al. A comparison of doxorubicin and COP for maintenance of remission in cats with lymphoma. J Vet Intern Med 10:372-375, 1996.
13. Rassnick KM, et al. MOPP-AC for treatment of lymphoma in cats, Proceedings from the 21st Annual Veterinary Cancer Society Meeting, p 10, 2001.
14. Rassnick KM, et al. Prognostic value of argyrophilic nucleolar organizer region (AgNOR) staining in feline intestinal lymphoma. J Vet Intern Med 13:187-190, 1999.
15. Teske E, et al. Chemotherapy with cyclophosphamide, vincristine, prednisolone (COP) in cats with malignant lymphoma: New results with an old protocol. J Vet Intern Med 16:179-186, 2002.
16. Vail DM, et al.: Feline lymphoma (145 cases): Proliferation indices, CD3 immunoreactivity and their association with prognosis in 90 cats receiving therapy. J Vet Intern Med 12:349-354, 1998.
17. Hematopoietic Tumors in Withrow SJ and MacEwen EG, Small Animal Clinical Oncology 2nd Edition, WB Saunders Co, Philadelphia, Pennsylvania, 1996, page 478.
18. Zwahlen, et al. Results of chemotherapy for cats with alimentary malignant lymphoma: 21 cases (1993-1997). J Am Vet Med Assoc 213:1144-1149, 1998.