

UPDATE ON FERRET LYMPHOMA AND CHEMOTHERAPY



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What IS lymphoma?

- ▣ Lymphoma is a cancer of the white blood cells called lymphocytes. Many people use the phrases lymphoma and lymphosarcoma as synonyms.
- ▣ White blood cells have access to almost the entire body – therefore, lymphomas can appear virtually anywhere in the body as well.



Occurrence

- ▣ Lymphoma is considered to be the third most common neoplasm in ferrets after adrenal disease and insulinoma.
- ▣ It is difficult to fully assess incidence due to a lack of consistency in diagnosis. Accurate diagnosis is ESSENTIAL! Many ferrets are misdiagnosed.
- ▣ Several forms appear to exist, but the underlying cause of lymphoma remains unknown.



Forms of Lymphoma

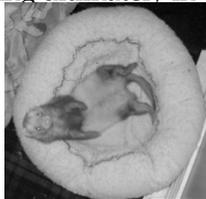
- ▣ One form is the lymphoblastic form (also known as juvenile), which is most commonly seen in ferrets under the age of 3 years.
- ▣ Characterized by infiltration of the visceral organs by lymphocytes. Presentation is typically a young ferret in respiratory distress – usually secondary to enlargement of the thymus.



Forms of Lymphoma

- ❑ Second form is lymphocytic (adult onset) seen in ferrets over 3 years of age.
- ❑ Presentation for these animals is a “healthy” ferret with enlarged peripheral lymph nodes. Eventually, these lymphocytes also invade internal organs, resulting ultimately in organ failure.

“Lucy” is under treatment for lymphoma currently - as of 11/02/08



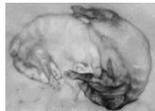
Immunohistochemistry

- ❑ Perhaps more usefully, lymphomas can be classified as being of B- or T-cell origin by detecting specific cell based antigens.
- ❑ A recent study (Onuma et al) indicated that 88.9% of examined ferret specimens were T-cell origin, while 11.1% were B-cell origin.
- ❑ In dogs and people, T-cell lymphomas are more resistant to chemotherapy and therefore have a poorer prognosis. However, this is not true in cats, and we don't know the implication in ferrets.



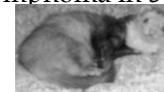
Cytomorphologic Grading

- ❑ Additionally, lymphomas can be analyzed and graded by their cytologic features.
- ❑ Low grade neoplasms demonstrate small lymphocytic cells with few mitotic features.
- ❑ Intermediate grade lymphomas are classified as diffuse large cell lymphoma.
- ❑ High grade lymphomas are classified as diffuse immunoblastic lymphoma with larger numbers of mitotic figures.



Site of Origin Classification

- ❑ In a study done by Onuma et al involving 29 ferrets - lymphoma was classified by location:
 - ❑ Multicentric was present in 40% of the cases
 - ❑ Gastrointestinal present in 45% of the cases
 - ❑ Mediastinal present in 10% of the cases
 - ❑ Cutaneous lymphoma in 5% of the cases
- ❑ 27 of 29 had concurrent adrenal disease



Diagnosis of Lymphoma

- ❑ Lymphoma is widely over-diagnosed in ferrets!
- ❑ The only way, in almost all cases, to diagnose lymphoma is a full thickness biopsy.
- ❑ Lymphoma cannot be diagnosed by physical examination, blood work, ultrasound, or in many instances – needle aspirates.
- ❑ Lymphoma is a systemic disease – it requires a systemic approach.
- ❑ Lymphoma is much more difficult to diagnose in ferrets than in dogs and cats.



Enlarged Peripheral Lymph Nodes

- ❑ Many, many ferrets have been diagnosed as having lymphoma by the finding of “enlarged peripheral lymph nodes”.
- ❑ Beware!! This is a common site of fat deposition in the ferret! Even remarkably big swellings in the region of the lymph nodes can be normal!
- ❑ NO ferret should ever be diagnosed based on physical examination only!



Lymphoma is the Great Impersonator

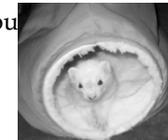
- ❑ Lymphoma can look like almost any disease. It should be included on the differential list of any sick ferret.
- ❑ The signs of lymphoma can always be caused by other diseases as well. Don't jump to a fatal diagnosis. Lymphoma MUST be diagnosed by biopsy, in addition to a thorough work up.



“Oly” – I’m not a ferret. But, I play one on TV!

Minimum Data Base and Staging for Therapy

- ❑ A MDB is necessary to properly stage lymphoma as well as to ensure an accurate diagnosis. This includes:
- ❑ -Complete Blood Count/Platelet Count
- ❑ -Chemistry Profile
- ❑ -2 view whole body radiographs
- ❑ -Abdominal ultrasound
- ❑ -Affected organ tissue biopsy / popliteal node biopsy
- ❑ -Bone marrow aspirate



Staging Criteria

- ❑ Lymphoma can be defined by the following 4 stages:
- ❑ Stage 1 - Tumor involves only a single site
- ❑ Stage 2 - Multiple sites are involved on the same side of the diaphragm
- ❑ -Stage 3 - The spleen and lymph nodes on both sides of the diaphragm are involved
- ❑ Stage 4 - Multiple sites on both sides of the diaphragm are involved



Treatment Options

- ❑ Once a patient has been correctly diagnosed and staged, the available treatment options can be identified and evaluated.
- ❑ At this point in time, there is no evidence that indicates any one treatment is superior for the majority of cases. Controlled studies are lacking, and many clinicians have protocols with which they are most comfortable.



Reported Protocols

- ❑ Reported protocols that have been used include:
- ❑ COP and modified COP protocols
- ❑ Single agent Doxorubicin
- ❑ Combination Doxorubicin and Orthovoltage radiation
- ❑ High dose vincristine
- ❑ Single agent prednisone
- ❑ Tufts protocol



Survival Rates

- ❑ Most of the protocols reported do NOT have any data to support or negate their use. The sample sizes are simply too small for reasonable conclusions to be reached.
- ❑ Reports of mean survival times with treatment are all over the board, starting at 180 days for low grade lymphoma to 437 days for those treated with a very aggressive protocol. However, these sample sizes are still very small!

Currently, there is NO “magic bullet” for the treatment of lymphoma.



Most Commonly Used Protocols

- ▣ Although countless protocols have been tried, very few published reports are available, and even fewer controlled studies have been done.
- ▣ Historically – veterinarians have typically used one of 3 protocols as “starting points” for therapy: steroid treatment, modified COP protocols (derived from dog/cat medicine) and most recently, the “Tufts Protocol”.



Steroids Alone

- ▣ Primary treatment with steroids is a common form of therapy for a number of reasons: it is inexpensive, minimally invasive, and for many patients improves quality of life.
- ▣ At this point, there is no indication that steroids alone increase the survival period, disease free interval, or even induces remission in most patients.
- ▣ On the down side, it may be responsible for inducing multiple drug resistance in some animals.
- ▣ Many ferrets have already been “pre-treated” with steroids because of concurrent insulinoma, inflammatory bowel disease, or other steroid responsive conditions.



Steroid therapy

- ▣ At this time, it appears that steroid therapy is only appropriate for owners interested in disease palliation, or those wishing non-invasive or non-expensive treatment.
- ▣ Prednisone, prednisolone, or dexamethasone are indicated. Prednisolone may be preferred if hepatic involvement is suspected. Longer acting injectable steroids likely have limited use.



COP and Modified COP Protocols

- ❑ These protocols have largely been derived from successful protocols in treating dog and cat lymphomas, and are based on the assumption that ferret lymphoma follows the rule that lymphoma is a very drug sensitive neoplasia.
- ❑ The protocols are significantly more aggressive than steroids alone, and are also more invasive and expensive.
- ❑ Some data does indicate that they are effective in increasing the survival length, increasing the disease free interval, and inducing remission in a significant proportion of the patients.



Modified COP therapy

- ❑ Successful implementation of a modified COP protocol is more involved than similar protocols for dogs and cats.
- ❑ Pre-treatment CBC's may require sedation in some patients.
- ❑ Administration of some medications must be given IV without extravasation – for most patients, sedation or the surgical implantation of a venous port will be indicated.



Modified COP protocol published by N. Antinoff et al

Week	Drug	Dose
3 days	L-Asparaginase	400 IU/Kg SQ*
1	Vincristine Prednisone	0.12 mg/kg IV 1 mg/kg PO SID - continue throughout therapy
	Cyclophosphamide	10 mg/kg PO
2	Vincristine	0.12 mg/kg IV
3	Vincristine	0.12 mg/kg IV
4	Vincristine Cyclophosphamide	0.12 mg/kg IV 10 mg/kg PO
7,10,13 and so on	Vincristine Cyclophosphamide	0.12 mg/kg IV 10 mg/kg PO
Rescue:	Doxorubicin	1-2 mg/kg IV over 30 min

* Premedicate with diphenhydramine, 1-2 mg/kg 30 min prior to treatment

Additional COP considerations

- ❑ Recheck CBC prior to each treatment, and if leukopenic, postpone chemotherapy and recheck CBC in 5-7 days.
- ❑ If the patient cannot tolerate vincristine and cyclophosphamide together, they can be split apart by 10 days (maintaining the 3 week intervals)
- ❑ Dose reduction by 25% may be considered if undesirable side effects or leukopenia occur.



Success rate, COP protocol

- ▣ As with all lymphoma treatments discussed in this presentation – little data exists to support or negate the use of this protocol. However, it is very widely used in dog/cat medicine with significant success.
- ▣ The authors publishing this paper claim an improvement in nearly 85% of patients treated with this protocol.



Tufts Protocol



- ▣ This is a newer approach to lymphoma treatment in the ferret, aiming to maintain the good qualities of the previous therapies while minimizing the downsides.
- ▣ At this point, no published reports exist to substantiate the success of the protocol, but the author feels the response has been good.
- ▣ This protocol eliminates the use of IV medications, although regular blood counts are still necessary – several of the drugs are myelosuppressive.

Tufts Protocol

Week	Drug	Dose
1	L-asparaginase	10,000 IU/m2 SQ
	Cytosan	250 mg/m2 PO with 50mL/kg SQ LRS
2	Prednisone	2mg/kg PO SID X 7d
	L-asparaginase	10,000 IU/m2 SQ
	Prednisone	2mg/kg PO EOD
3	L-asparaginase	10,000 IU/m2 SQ
	Cytosar	300 mg/m2 SQ X 2d (diluted 100 mg in 1mL water)
4	CBC	
5	Cytosan	250 mg/m2 PO w/LRS
7	Methotrexate	0.8 mg/kg IM
8	CBC	
9	Cytosan	250 mg/m2 PO w/ LRS

Tufts Protocol con't

Week	Drug	Dose
11	Cytosar	300 mg/m2 SQ x 2d (diluted)
	Leukeran	1 Tab/ferret PO
12	CBC	
13	Cytosan	250 mg/m2 PO with LRS
15	Procarbazine	50 mg/m2 PO SID X 14d
16	CBC	
17	CBC	
18	Cytosan	250 mg/m2 PO with LRS
20	Cytosar	300 mg/m2 SQ X 2d (diluted)
	Leukeran	1 T/ferret PO SID X 2d
23	Cytosan	250 mg/m2 PO with LRS

Tufts Protocol con't

Week	Drug	Dose
26	Procarbazine	50 mg/m ² PO SID X 14d
27	CBC/Chemistry	

If not in remission - repeat weeks 20-26 for 3 cycles.

If CBC shows severe myelosuppression, reduce dosage by 25% for next treatment. Antibiotic therapy is indicated in suppressed patients!

Other potential side effects to monitor for include nausea, vomiting, and diarrhea. L-asparaginase can result in anaphylaxis.

The cytoxin elixir will usually need to be prepared by a compounding pharmacy (use the injectable form administered orally).

Grading Side Effects - Tufts Protocol

Toxic Effect and Grade	Signs
Neutropenia	
0	None
1	1,500-3,000 neutrophils
2	1,000-1,500 neutrophils
3	500-1,000 neutrophils
4	<500 neutrophils
Platelet deficiency	
0	None
1	100,000-200,000
2	50,000-100,000
3	15,000-50,000
4	<15,000

Additional Side Effects

Toxic Effect and Grade	Signs
Vomiting/Diarrhea	
0	None
1	Nausea, Inappetance, Soft Stool
2	Sporadic vomiting, anorexia <2 days, 1-4 watery stools/day for <2 days
3	1-5 vomiting episodes/day <2 days, anorexia for >3and<5 days, 4-7 watery stools/day for >2 days
4	Hospitalization for vomiting or diarrhea, anorexia for >5 days with 10% weight loss

How to calculate m² from weight

Kg	BSA	1.6	0.137
0.2	0.034	1.7	0.142
0.3	0.045	1.8	0.148
0.4	0.054	1.9	0.153
0.5	0.063	2.0	0.159
0.6	0.071	2.1	0.164
0.7	0.079	2.2	0.169
0.8	0.086	2.3	0.174
0.9	0.093	2.4	0.179
1.0	0.100	2.5	0.184
1.1	0.107	2.6	0.189
1.2	0.113	2.7	0.194
1.3	0.119	2.8	0.199
1.4	0.125	2.9	0.203
1.5	0.131	3.0	0.208

For more information

- ▣ The Tufts Protocol looks very promising – but additional case studies are needed to evaluate which side effects are seen most commonly and also to verify the effectiveness of the protocol.
- ▣ Interested veterinarians should contact Dr. Joerg Mayer at Tufts University School of Veterinary Medicine.



In Summary:

- ▣ Lymphoma is a devastating and common disease of ferrets.
- ▣ Right now, we don't have a consistent standard for diagnosis – which complicates matters.
- ▣ To make things even more confusing – treatments vary dramatically and no information is available to determine the effectiveness of the existing protocols.
- ▣ Bottom line: we don't really even know what we know – we need more information!

YOU can help!

- ▣ Owners interested in treating their pets and veterinarians willing to write up case reports are the key to finding the answers!



Questions?

