Lymphoma Diagnosis & Treatment

Simon Tappin

MA VetMB CertSAM DipECVIM-CA MRCVS
RCVS & European Specialist in Veterinary Internal Medicine
Dick White Referrals, United Kingdom
Introduction

What is lymphoma?
Why to animal get lymphoma?
Diagnosis
  • Staging
  • Prognostic indicators
Treatment options
  • Steroids
  • Chemotherapy
What is Lymphoma

Cancer of lymphocytes (white blood cells)
Lymphosarcoma / malignant lymphoma

One of the most common canine neoplasms

- Incidence 114 cases a year per 100,000 dogs
- Incidence increases with age
  - <1 year old 1.5 cases per 100,000 dogs
  - 10-11 year olds 84 cases per 100,000 dogs

Incidence in cats proportional to FeLV
Estimated 2% of referral institution caseload
Lymph Node Positions

- Parotid lymph node
- Retropharyngeal lymph nodes
- Tracheal duct
- Thoracic duct
- Cisterna chyli
- Superficial inguinal lymph nodes
- Popliteal lymph node
- Submandibular lymph node
- Prescapular lymph node
- Bronchial lymph nodes
- Axillary lymph node
- Mesenteric lymph nodes
Canine Lymphoma

**Histological classification**
- 66% high grade
- 28% intermediate grade
- 6% low grade

**Anatomical classification**
- Multicentric 84%
- Alimentary ≤ 7%
- Extranodal ≤ 7%
- Mediastinal ≤ 2%

**Sub-types**
- B-cell
  - Diffuse/multi-centric
  - T-cell-rich large B-cell
  - Marginal zone/low-grade
- T-cell
  - Diffuse/multi-centric
  - T-zone
  - Extranodal
  - Cutaneous
- Null-cell
What causes Lymphoma?

Genetic factors
- Breed predispositions
  - ↑ Risk: Boxers / Bassets / St Bernard's / Scotties / Airedales
  - ↓ Risk: Dachshunds / Pomeranians / Yorkies
- Chromosomal abnormalities

Environmental
- Urban vs Rural
- Herbicides
- Magnetic fields
- Tobacco smoke

Infectious causes
- FeLV / FIV
Feline Leukaemia Virus

FeLV causes Lymphoma in cats
Incidence markedly reduced with vaccination
  • Pre vacc 60-70% lymphoma FeLV +
  • Post vacc 10-20% lymphoma FeLV +
FeLV gives rise mostly to multi-centric & mediastinal LSA
FeLV seen in younger cats
Decreased incidence changed pattern of LSA in cats
# Feline Lymphoma

<table>
<thead>
<tr>
<th>Site</th>
<th>Frequency</th>
<th>Age</th>
<th>T-Cells</th>
<th>FeLV</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIT</td>
<td>50-70%</td>
<td>10 - 14</td>
<td>High</td>
<td>Low (5%)</td>
</tr>
<tr>
<td>Multicentric</td>
<td>10-25%</td>
<td>α to FeLV</td>
<td>α to FeLV</td>
<td>Approx 1/3</td>
</tr>
<tr>
<td>Thymic</td>
<td>10-20%</td>
<td>Young</td>
<td>High</td>
<td>High &gt;80%</td>
</tr>
<tr>
<td>Nasal</td>
<td>10%</td>
<td>Aged</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Renal</td>
<td>5-10%</td>
<td>Middle age</td>
<td>Low</td>
<td>Low-Mod</td>
</tr>
<tr>
<td>Other</td>
<td>5-25%</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Mixed</td>
</tr>
</tbody>
</table>
Clinical Signs

- Enlargement of lymphoid tissue
  - Lymph node enlargement
    - Lymphadenopathy
  - Splenic enlargement
    - Splenomegaly
  - Hepatic enlargement
    - Hepatomegaly
Clinical Signs

Reduced function of normal tissue

- Bone marrow involvement
  - Anaemia
  - Decreased platelets (thrombocytopenia)
  - Decreased neutrophils (neutropenia)
- Gastrointestinal Lymphoma
- CNS Lymphoma
- Renal Lymphoma
- Mediastinal Lymphoma
- Cutaneous Lymphoma
  - Mycosis Fungoides
- Ocular Lymphoma
Diagnosis

Cytology – fine needle aspirates (FNA’s) Biopsies Imaging Staging (prognostic and treatment information)

• Thoracic radiographs
• Abdominal Ultrasound
• Bone marrow biopsy
Adjunctive Tests

Histopathology

  Immuno-histochemistry

  B-cells CD79a / T-cells CD3+

Thymidine Kinase

  Enzyme needed for cell division & not normally released into serum

  Increased levels specific for LSA

PARR

  Test of T-cell clonality

  Blood Lymphocytes + in grade III LSA

  Not correlated to Prognosis
Markers of a Poorer Prognosis

- WHO stage V
- Sub-stage b
- T cells
- Hypercalcaemia
- Pre-treatment with steroid
- Males
- High proliferation rate
- Cranial mediastinal mass
- High histology grade
Markers of a Poorer Prognosis

WHO stage V
Sub-stage b
T cells
Hypercalcaemia
Pre-treatment with steroid
Males
High proliferation rate
Cranial mediastinal mass
High histology grade
WHO Staging

Stage I
  Single LN
Stage II
  Multiple LNs in one area
Stage III
  Generalised lymphadenopathy
Stage IV
  Generalised lymphadenopathy
  Liver and spleen involvement
Stage V
  Bone marrow involvement or non lymphoid organ involvement e.g. CNS

Sub-Stages

a – Well / no clinical signs
b – Ill / clinical signs
Markers of a Poorer Prognosis

WHO stage V
Sub-stage b
T cells
Hypercalcaemia
Pre-treatment with steroid
Males
High proliferation rate
Cranial mediastinal mass
High histology grade
Markers of a Poorer Prognosis

- WHO stage V
- Sub-stage b
- T cells
- Hypercalcaemia
- Pre-treatment with steroid
- Males
- High proliferation rate
- Cranial mediastinal mass
- High histology grade
Markers of a Poorer Prognosis

WHO stage V
Sub-stage b
T cells

**Hypercalcaemia**
Pre-treatment with steroid
Males
High proliferation rate
Cranial mediastinal mass
High histology grade
Markers of a Poorer Prognosis

WHO stage V
Sub-stage b
T cells
Hypercalcaemia
**Pre-treatment with steroid**
Males
High proliferation rate
Cranial mediastinal mass
High histology grade
Markers of a Poorer Prognosis

WHO stage V
Sub-stage b
T cells
Hypercalcaemia
Pre-treatment with steroid

Males
High proliferation rate
Cranial mediastinal mass
High histology grade
Markers of a poorer Prognosis

WHO stage V
Sub-stage b
T cells
Hypercalcaemia
Pre-treatment with steroid
Males
High proliferation rate
Cranial mediastinal mass
High histology grade
Markers of a Poorer Prognosis

WHO stage V
Sub-stage b
T cells
Hypercalcaemia
Pre-treatment with steroid
Males
High proliferation rate
Cranial mediastinal mass
High histology grade
Markers of a Poorer Prognosis

- WHO stage V
- Sub-stage b
- T cells
- Hypercalcaemia
- Pre-treatment with steroid
- Males
- High proliferation rate
- Cranial mediastinal mass

**High histology grade**
Treatment

Untreated dogs succumb in 4-6 weeks
Lymphoma is very responsive to chemotherapy
  • 90% of dogs will respond
  • 70% of cats will respond
Median survival time (MST) depends on protocol
  • Steroids alone – 8-12 weeks
  • COP – 6 months
  • Doxorubicin alone – 7 months
  • Madison-Wisconsin – 12-18 months
Chemotherapy

- Lymphoma is a systemic disease therefore systemic treatment
- Lymphoma is very responsive to chemotherapy
- Chemotherapy drugs damage DNA
  - Preventing cell division or inducing apoptosis
  - Affects cells dividing quickest the most
  - Affects neoplastic cells more than normal cells as they often lack repair mechanisms
- Chemotherapy well tolerated in animal at doses utilised
  - Used to palliate clinical signs rather than cure disease
  - 90% of owners would treat a dog again with chemotherapy for lymphoma if placed in the same situation
Safety of Chemotherapy

Occupational Exposure is Significant

• Human nurses increased levels in urine
• Similar exposure also seen in veterinarians
• Reduce administration risks by:
  • Wear protective clothing
  • Used laminar flow cabinet for reconstitution
  • Dispose of waste appropriately

Risks to Owners

• Excretion in Faeces and Urine dependant on the agent used
  • Care clearing up for first 72 hours
• Not to handle tablets directly
• Risks greatest in pregnancy / immuno-suppressed
  • e.g. HIV+ or Elderly owners
Giving Chemotherapy
Preparing Chemotherapy
Giving Chemotherapy
Which is the best drug to use?

- All drugs induce drug resistance, combinations reduce the speed this occurs
- Combinations of drugs that work in different ways, increases the number of cells targeted when the population is varied
- Owners wishes / expectations very important as well as efficacy
  - Costs vary widely
    - 12 months of treatment with COP ≈ £1500-2000
    - Full 25 Week Madison-Wisconsin protocol ≈ £3-4000
- Some protocols very ‘owner intense’ with frequent visits need
- For example fractious or aggressive animals, might be better with tablet only or single agent doxorubicin (q3 weeks)
- CNS disease need to use drugs which cross the BBB
  - CCNU / Cytarabine
How frequently do I give the drugs?

**Dose Intensity Chemotherapy**
- Uses the maximal tolerated dose and the shortest period possible between doses
- Dose reductions of 20% can reduce efficacy by up to 50%
- Dosage calculated proportionally to BSA in do rather than weight (thought to more accurately reflects metabolism – although controversial in animals <15kg)

**Metronomic Chemotherapy**
- Smaller but more frequent dosing
- Targets the growing vascular supply to the tumour, thus reduces tumour growth is not very applicable to LSA (useful for HSA)
Chemotherapy for Lymphoma

Catabolic steroid
Inhibits DNA synthesis
Directly toxic to lymphocytes
Also anti-inflammatory
Cheap / well tolerated
SE PU/PD, polyphagia, weight changes, GIT ulceration etc
Chemotherapy for Lymphoma

- Prednisolone
- Vincristine
- Cyclophosphamide
- Doxorubicin
- L-Asparaginase
- CCNU

Derived from periwinkle
Inhibits the formation of microtubules
These are needed for cell division
Given by intravenously
Metabolised by the liver
Excreted in faeces
Chemotherapy for Lymphoma

Prednisolone
Vincristine
Cyclophosphamide
Doxorubicin

Alkylating agent
Bind DNA & introduce an alkyl group
Stops transcription, replication & repair
Cheap – relatively well tolerated
Urinary excretion
SE: Haemorrhagic cystitis
Chemotherapy for Lymphoma

Prednisolone
Vincristine
Cyclophosphamide
Doxorubycin
L-Aspariginase
CCNU

Multiple actions
- Intercalates DNA
- Inhibits DNA replication
- Inhibits protein synthesis
- Forms free radicals

Given as i/v infusion
Care with catheter
SE: DCM, HS, nephrotoxic in cats
Chemotherapy for Lymphoma

Prednisolone
Vincristine
Cyclophosphamide
Doxorubicin
L-Aspariginase
CCNU

Bacterial enzyme that degrades asparagine
Stops cells growing
Inhibits protein synthesis
Normal cells make asp.
Resistance relatively easy as select for cells will up regulated asparagine synthetase
Chemotherapy for Lymphoma

Prednisolone
Vincristine
Cyclophosphamide
Doxorubicin
L-Asparaginase
CCNU

Alkylating agent
Bind DNA & introduce an alkyl group
Stops transcription, replication & repair
Expensive and moderately toxic
  Profoundly myelosuppressive
  Hepatotoxic
COP Protocol

Cyclophosphamide, Vincristine (O – Oncovin) and Prednisolone
Most commonly used Chemotherapy protocol used in SAP for LSA
Relatively Cheap, ‘easy’ and well tolerated

**Induction (8 weeks)**

- Cyclophosphamide 50mg/m² po for the 1st 4 days of each week
- Vincristine 0.5mg/m² iv q7 days
- Prednisolone 40mg/m² po SID for 7 days then 20mg/m² EOD with Cyclophosphamide
COP Protocol - Maintenance

**Maintenance (2-6 months)**
- Vincristine 0.5mg/m² iv q14 days
- Cyclophosphamide + Prednisolone given for the first 4 days of every other week

**Maintenance (6-12 months)**
- Vincristine 0.5mg/m² iv q21 days
- Cyclophosphamide + Prednisolone given for the first 4 days of each third week

**Maintenance (12 - 18 months)**
- Vincristine 0.5mg/m² iv q28 days
- Cyclophosphamide + Prednisolone given for the first 4 days of each fourth week
Madison-Wisconsin Protocol

Considered the ‘Gold Standard’ chemotherapy for LSA

Uses Vincristine, Cyclophosphamide, Prednisolone, Doxorubicin and L-asparaginase

Many variations but standard protocol is 25wks

| Drug        | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
|-------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Pred        | ● | ● | ● | ● |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| L-Asp       | ● |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Vincristine | ● | ● | ● | ● | ● |● |● |● |● |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cyclophos   | ● |   |● |● |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Doxo        |   | ● |● |● |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
Rescue Protocols

• Subsequent remissions can be achieved
  • Usually harder to achieve
  • Usually for shorter periods
• Repeating the induction protocol
  • Achieved in approx 50% of patients
  • Period of approx 50% of 1\textsuperscript{st} remission
• Maintenance free protocol longer 2\textsuperscript{nd} remission periods
• Rescue protocols
  • MOPP
  • Doxorubicin
  • CCNU
Complications of Chemotherapy

Drugs affect all cells in the body
Affects those dividing quickest the most
Side effects occur as a result of these cells being affected
Side effects seen in about 10% of patients

- Bone marrow – decreased white blood cells / Platelets
- Hair follicles – Dogs and cats don’t loose hair (c.f. people) however whiskers sometimes fall out and hair re-growth may be poor
- GUT – vomiting and diarrhoea are common as a result of drug administration. Nausea is also common in people, but harder to recognise in animals.
Specific Complications

- Extra-vascularisation
  - Local irritation around injection site
  - Vincristine & Doxoribucin
- Haemorrhagic cystitis
  - Cyclophosphamide
  - Breakdown product Acrolein toxic to bladder
- DCM – Doxorubicin / Mitoxantrone
- Anaphylaxis/ Hypersensitivity – L-asparaginase
Any Questions?