Do Palliative Steroids Prolong Survival in Dogs With Multicentric Lymphoma?

A Knowledge Summary by

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KNOWLEDGE SUMMARY

PICO question

In dogs with naturally occurring multicentric B cell lymphoma does treatment with glucocorticoids alone extend survival time when compared to no treatment?

Clinical bottom line

There is weak evidence, due to insufficient studies with untreated control groups, regarding the impact on survival of prednisolone treatment in dogs with multicentric lymphoma.

From the papers identified from the search functions used for the clinical question remission in uncontrolled trials was reported following prednisolone treatment. Details of which can be found in other sections of this paper.

Clinical Scenario

An eight year old male neutered Labrador presents with multicentric lymphadenopathy. He is otherwise well. Staging (abdominal and thoracic imaging plus bone marrow aspirates) confirm that he is stage 3a (multicentric lymph node involvement without evidence of systemic illness). Routine bloods are normal. The owner does not want to use chemotherapy due to the health and safety implications. You have offered prednisolone treatment and explained the side effects. The owner would like to know the prognosis and average survival time if she opts for treatment with prednisolone alone.

Summary of the evidence

Valli (2013)	
Population:	Dogs with lymphoma recruited via Veterinary Cancer Society 2006-2008 and with confirmed histopathology
Sample size:	944 dogs with lymphoma. Survival data only available for 456 dogs.
Intervention details:	Dogs with lymphoma of varying types (high grade, intermediate grade and low grade) treated with various types of chemotherapy or with prednisolone alone or not treated. Drug doses and duration are not specified. The paper does not state how many dogs were in each of the lymphoma type groups, however there is limited reference to the numbers of dogs in some of the treatment groups. This reflects the focus on survival for the group as a whole rather than in respect of differing treatment regimes.
Study design:	Descriptive case series (retrospective)
Outcome studied:	Survival in days
Main findings: (relevant to PICO question):	Proportional hazards regression models were used to assess relative risk of death and reported as Hazard ratios (HR) and 95% Confidence

	Intervals (CI). The numbers of dogs in each treatment group (chemotherapy including hydroxydaunorubicin, chemotherapy without hydroxydaunorubicin, prednisone alone and no treatment) was not stated for any of the lymphoma types. • High Grade T and B cell lymphoblastic lymphomas (n= 36) with possible prednisolone only treatment. States that there is no evidence that prednisolone alone is better than no treatment (HR 0.50; 95% CI, 0.064-3.90; p=0.51). Centroblastic B cell lymphomas (n= 186). Risk of death of dogs treated with prednisolone alone similar to that with no treatment (HR 1.65;95%CI, 0.56-4.87; p=0.36). • Immunoblastic B cell lymphomas (n= 57). Prednisolone only therapy associated with poorer survival than chemotherapy (HR 47.22 CI95% 2.67-834.74 p=0.009) but 0 dogs in this group were were in the no treatment group. • This paper also compared treatment to histological grade of lymphoma. The numbers of dogs in this part of the analysis was not stated. Survival following the different treatments (chemotherapy including hydroxydaunorubicin, chemotherapy without hydroxydaunorubicin or prednisone alone) was compared to that of dogs that received no treatment. • Low grade lymphomas (n=81) were treated with chemotherapy including hydroxydaunorubicin, chemotherapy without hydroxydaunorubicin , prednisone alone and no treatment however the numbers in each group were not stated. However those treated with prednisone only had increased risk of death (HR 40.57 6.8-242.09 P <0.001) compared to dogs receiving no treatment. • Intermediate grade lymphomas (n=242): dogs treated with prednisolone only (HR 1.920.68-5.39 p = 0.22) showed no significant difference from those not treated. Dogs treated with chemotherapy including hydroxydaunorubicin or chemotherapy without hydroxydaunorubicin , showed a reduced risk of death • High grade lymphomas (n=103) treated with prednisolone only (HR 1.63 95% CI 0.53-5.03 p=0.39) showed no significant difference compared to chemotherapy including hydroxydaunorubicin, chemotherapy without hydroxydaunorubicin and no treatment) was not stated. Based on this study prednisone only showed no advantage over no treatment for dogs with diffuse large centroblastic B cell lymphoma. Across all grades of lymphoma (including some T cell lymphoma dogs) treatment with prednisolone alone increased the risk of death but this increase was only significant when compared to chemotherapy treatment with or without hydroxydaunorubicin and not when compared to the no treatment group.
Limitations:	• The paper is a retrospective study assessing a wide variety of aspects of dogs with histologically confirmed lymphoma.

	These include classification of cell type (T vs B, mitotic rate and histological types.) It aims to show how survival varies in different treatment regimens and relate this to disease variables. • Cases were recruited through a Veterinary Cancer Society newsletter which could result in loss of patients from veterinary practices without a special interest in cancer treatment which would mean there might be fewer patients in the prednisolone alone or no treatment groups. There was an ongoing study into one treatment regime so this may have been over-represented. • The authors state that the majority of cases came from the USA with a few from Europe and Canada. It is possible that there were variations in treatment choices or histological diagnosis in the cases from Europe however there is no detail provided about the patient numbers involved. • Patients were only included where there was histological confirmation and immunohistochemistry had been performed. Again this might reduce recruitment of patients whose owners were unwilling or unable to perform these tests or where a diagnosis was reached by cytology alone. • Survival time was recorded for all patients and those who remained alive at the time of the study were censored. • As this was a retrospective study, patients were allocated to a particular treatment option based on clinician and owners preference. It is not clear from the paper if cases from particular practices or regions had differing treatment regimes. • There is no reporting of the dose of prednisolone used for the prednisolone alone group or any reporting of the chemotherapy doses used. • Similarly there is no reporting of the numbers of dogs in each treatment group within each category. This reflects the focus on survival for the group as a whole rather than in respect of differing treatment regimes.

Tozon (2006)	
Population:	Dogs with lymphoma diagnosed by cytology
Sample size:	39 dogs
Intervention details:	13 dogs on differing chemotherapy regimes: COP protocol (n=6), COPA protocol (n=4) doxorubicin (n=2) and methylprednisolone (n=1). Drug doses and duration were not stated
Study design:	Descriptive case series
Outcome studied:	Occurrence of different cyto-morphological diagnoses and how sex, clinical stage and treatment choice affects first remission time (days) and survival time (days) of patients undergoing differing regimes of treatment.

Main findings: (relevant to PICO question):	Cytomorphological analysis was similar to previous reports with high malignant lymphoma in 25 dogs, intermediate grade lymphoma in 13 dogs and low malignant lymphoma in 1 dog. There is no information on outcome in 26 dogs and it is not clear if they received any treatment. 13 dogs were treated these comprised 6 dogs with high grade, 6 dogs with intermediate and 1 dog with low grade. Details on which treatment each dog received are provided but the numbers in each subgroup are two small to draw any further information on the survival times associated with each lymphoma type. However within all grades of tumour treated median survivals were: COP-treated dogs (n=6) 160 days, COPA treated dogs (n=4) 225 days Doxorubicin treated dogs (n=2) were alive at 90 days Methylprednisolone alone (n=1) 240 days Median first remission was longer in females (n= 6; 215 days) than males (n=7; 159 days)
Limitations:	• Only one patient out of 39 received prednisolone alone. • Authors do not state how cases were selected or give any inclusion or exclusion criteria for this study

Brick (1968)	
Population:	Dogs and cats with lymphoma examined at Ohio State University Veterinary Clinic 1959-1965
Sample size:	32 dogs and 6 cats
Intervention details:	Comparison of 4 different treatment regimens: cyclophosphamide (n=4 dogs), prednisolone alone (n=6 dogs), chlorambucil (n=9 dogs), chlorambucil combined with prednisolone at the same doses as the individual drugs (n=7 dogs) and no treatment (n= 6 dogs) on mean survival time. The following dosage regimes were used: Cyclophosphamide 0.3mg/kg/day for 14 days followed by 14 days with no treatment Prednisolone 0.5mg/kg/day for 14 days followed by 7 days without treatment and the schedule then repeated. Chlorambucil 0.2mg/kg/day for 14 days followed by 14 days without treatment and the schedule then repeated. Prednisolone 0.5mg/kg/day for 14 days followed by chlorambucil 0.2mg/kg/day for 14 days and the schedule then repeated.
Study design:	Descriptive case series
Outcome studied:	Objective – Survival time in weeks
Main findings: (relevant to PICO question):	• 6 dogs were given no treatment and mean survival time was 2.5 weeks and disease was extensive in 4 of the dogs. However grade was not mentioned. • Prednisolone regime was administered to 6 dogs however one of these also received radiotherapy on one occasion. Survival time ranged from 1-7.5 months with a mean of 2.5 months. • Of the 6 dogs and 2 cats that received prednisolone alone only 7 had a temporary reduction in node size.
Limitations:	• The paper is a retrospective study but does not state how patients were identified or if any cases were excluded. • Diagnosis was based on a combination of clinical signs (anorexia, depression, weight loss, anaemia and generalized lymphadenopathy) haematology results and a biopsy of tonsil or popliteal lymph node or bone marrow which would be acceptable assuming all patients had all three criteria assessed. This is not stated in the paper. Furthermore the paper does not state whether dogs had all or some of these symptoms and whether there was a difference in the presentation of dogs and cats. • The paper does not specify the stage/sub stage of the cases reported except to state that the patients that had no treatment had widespread disease. • Mean survival was reported rather than median which given the low numbers of cases is far from ideal.

	• Paper does not state the survival time of 1 dog that also received radiation therapy and does not state which of the 6 dogs and 2 cats did not get a reduction in node size. There is no indication if location or grade of disease affected this finding. • Regime is not continuous prednisolone as usually recommended in current veterinary practice across the world.

Squire (1973)	
Population:	Dogs with naturally occurring lymphoma recruited from local veterinary practices.
Sample size:	100 dogs.
Intervention details:	Comparison of 4 different chemotherapeutic treatment schedules : 1. Prednisone 2 mg/kg/day orally for 7 days followed by 1 mg/kg/day thereafter (n=49) 2. Prednisone as above plus cyclophosphamide 5 mg/kg/day orally for 7 days followed by 2.5 mg/kg thereafter (n=34) 3. Vincristine 0.03mg/kg intravenously on day 1 and 8. Prednisone 1 mg/kg/day orally on days 1 and 8 and days 9-21. Cyclophosphamide 5 mg/kg/day on days 2-7. Regime repeated every 14 days (n=19) 4. Vincristine 0.03mg/kg intravenously on day 1 and 8. Prednisone 2 mg/kg/day orally on days 1 and 8 followed by 1 mg/kg/day on days 9-21. Cyclophosphamide 5 mg/kg/day on days 15-21. 6-mercaptopurine 5 mg/kg/day on days 15-21. Regime repeated every 30 days (n=25) Dogs that failed to respond to one regime were moved to treatment schedules 2 or 3 and then reported in that group
Study design:	Non-randomised controlled trial
Outcome studied:	Mean objective remission duration in days (number of days before regime failed to maintain complete remission (CR) or partial remission (PR) despite drug-induced toxicity. Survival measured as number of days from initial presentation until natural death or euthanasia in terminal disease.
Main findings: (relevant to PICO question):	• This study excluded 18 dogs that died or were euthanased due to advanced disease or an unsatisfactory response to therapy within 14 days of admission from the survival and remission duration data. • Of the 49 dogs on prednisolone only 20 (41%) achieved complete remission with a mean objective remission time of 53 days (range 14-210 days). Remission induction rapid and usually reached its maximum at 7 days but was often partial within 72h. Partial remissions were not reported.

	• In 34 dogs on schedule 2, 13 achieved complete remission with a mean objective remission time of 62 days (range 17-130 days). 25 dogs had previously received prednisolone alone. 7 that that had failed to achieve remission with prednisolone alone showed some sensitivity but the objective remission time is not stated. 2 dogs failed to respond to schedule 2 despite achieving complete remission with prednisolone alone • In 19 dogs on schedule 3, 15 achieved complete remission with a mean objective remission time of 184 days (range 30-282 days). 14 of these dogs had previously received prednisolone alone or schedule 2. • In 25 dogs on schedule 4, 19 achieved complete remission with a mean objective remission time of 136 days (range 18-300 days). None had received prior treatment • No severe side effects reported except in 1 dog which developed a gastric ulcer after several months of treatment. • In several patients polyuria and polydipsia necessitated a reduction in dosage to 0.25-0.5 mg/kg/day. • Increased appetite and mild signs of Cushing's syndrome were noted in several animals (number not stated) • 9 dogs that failed to achieve remission on prednisolone alone were then treated with schedule 2. 7 of these dogs responded and 2 of these dogs failed to respond to schedule 2. • 14 dogs that failed to respond to prednisolone alone or to schedule 2 were treated with schedule 3. Of these 12 achieved complete remission. • Dogs on prednisolone alone were subsequently given chemotherapy if response was unsatisfactory or when refractoriness developed.
Limitations:	• Stage of lymphoma was defined as one of 4 stages (Stage 1 = one lymph node or one anatomic location • Stage 2 = involvement of multiple lymph nodes but limited to one side of the diaphragm • Stage 3 generalized involvement but limited to lymphoid tissue • Stage 4 involvement of any non-lymphoid tissue including viscera or blood or bone marrow nervous system etc. Viscera would normally be classed as stage 4 on the WHO system and the other areas would be as stage 5 on the WHO system Definition of Stage 3 in this study was generalised involvement but limited to lymphoid tissues i.e. lymph nodes, spleen, tonsils, thymus. In the current staging system this would be a group containing Stage 3 and Stage 4 patients. • Only included animals surviving to 14 days. 18 died or were euthanised due to advanced disease or an unsatisfactory response to therapy. • Doesn't state which of the prednisolone alone group went on to get chemotherapy and if this was taken into account in

	the survival times. However as there are no survival times given for this group we assume that most went onto get other treatments. • Mean remission duration is provided rather than median. Given the extremely wide range of 14-210 days this is far from ideal. • No data on patients who did not get treatment as patients were recruited to be part of this study and given a treatment regime.

Appraisal, application and reflection

There is limited data on this topic with papers reporting findings in relatively small numbers of dogs. Unfortunately the paper that most closely answers the clinical question (Mortier et al., 2012) was only available as an abstract and therefore could not be fully reviewed. This study suggested that dogs could achieve remission for up to 210 days on prednisolone alone (median of 32 days). This is similar to the findings of Brick et al. (1968) and their reported survival times of 1-7.5 months with a cyclical administration of prednisolone (0.5 mg/kg/day for 14 days followed by 7 days without treatment and with a schedule repeat). Squire et al. (1973) also reported remission times of 14-210 days with administration of 2 mg/kg/d for 7 days, then 1 mg/kg/d thereafter in 20 dogs (41%) who achieved remission for a mean of 53 days (range 14-210 days). In the latter paper they excluded patients who failed to survive 14 days so their median remission time is likely to be lower than their reported mean suggests. In addition Squire et al. (1973) do not report overall survival time however it can be assumed that this is longer than remission time. The single relevant case reported by Tozon et al. (2006) survived 240 days with Stage 3a lymphoma. The most recent publication (Valli et al., 2013) suggests that there is no benefit of treatment with prednisolone alone in a number of histological types and grades of lymphoma.

Clearly more research is required to review survival times of dogs with lymphoma who are given no treatment of any sort and comparing them to those receiving a standardised regime of prednisolone without prior other treatments and no further treatment of any sort being applied at a later date.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts (1973-week 32 2017) and PubMed NCBI (1968-August 2017)
Search terms:	CAB Abstracts 1 (lymphoma* or lymphosarcoma*).mp. or lymphoma/ or lymphosarcoma/ (CABI 14164) 2 (dog or dogs or canine).mp. or dogs/ or canis/ (CABI 196531) 3 (glucocorticoid* or prednisolon* or prednison*or steroid* or cortico-steroid* or corticosteroid).mp. or exp glucocorticoids/ or exp prednisolone/ or exp prednisone/ or steroids/ or corticoids/ (CABi 69157) 4 1 and 2 and 3

	PubMed 1 dog or dogs or canine 2 glucocorticoid or prednisolone or prednisone or steroid or cortico-steroid or corticosteroid 3 lymphoma or lymphosarcoma 4 1 and 2 and 3
Dates searches performed:	**23/08/2017**

Exclusion / Inclusion Criteria	
Exclusion:	• Wrong species, • Not lymphoma, • In vitro studies, • T cell lymphoma or wrong location of B cell lymphoma, • No treatment reported • Only chemotherapy or other treatments reported • No survival data reported • Reviews of other reported literature • Letters to editor • Conference proceedings with no abstract available • Available in English
Inclusion:	Correct species, B cell lymphoma with group treated with prednisolone alone and survival data reported in any form

Search Outcome

Database	Number of results	Excluded – not relevant to PICO question	Excluded – No survival data reported	Excluded – Reviews and letters	Excluded – not in English or not available	Total relevant papers
CAB Abstracts	260	231	1	7	17	4
PubMed	201	194	1	3		3
Total relevant papers when duplicates removed						**5**

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

1 Brick J., Roenigk, W. and Wilson, G. (1968) Chemotherapy of malignant lymphoma in dogs and cats. Journal of the American Veterinary Medical Association 153 (1) 47-52

2 Mortier,F., Daminet, S., Vandenabeele, S. et al. (2012) Canine lymphoma: a retrospective study (2009-2010). Vlaams Diergeneeskundig Tijdschrift 81 (6) 341-351

3 Squire, R., Bush, M., Melby, E. et al. (1973) Clinical and pathological study of canine lymphoma: clinical staging, cell classification and therapy. Journal of the National Cancer Institute, 51 (2), 565-74

4 Tozon, N., Samardzija, P., Prijic, S. et al (2006) Canine lymphoma: cytologic study and response to therapy. Slovenian Veterinary Research 43 (3) 127-133

5 Valli, V., Kass P., San Myint, M. et al. (2013) Canine lymphomas: association of classification type, disease stage, tumor type, disease stage, tumor subtype, mitotic rate, and treatment with survival. Domestic Mammal Disease 50 (5) 738-748 DOI: http://dx.doi.org/10.1177/0300985813478210

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