



The Pet Oncologist

Helping Vets With Pet Cancer Care

SAMPLE CONSULTATION REPORT

DATE: Friday 3rd January 2020
PET: George, 11-year-old MN DSH, 3.7 kg (BSA = 0.239 m²)
VET: XXX
PRACTICE: XXX
DIAGNOSIS: Renal lymphoma

SUMMARY OF FINDINGS:

George presented two days ago with acute dysuria. Physical exam revealed pale mucous membranes, renomegaly, and a grade IV/V systolic heart murmur. Hematology and serum biochemistry revealed moderate non-regenerative anaemia (HCT 18.6), moderate neutrophilia (32.95), mild monocytosis (2.24), and moderate renal azotaemia (urea 18.6, creatinine 313). Urinalysis revealed an inactive sediment. Urine C&S is pending. Abdominal ultrasonogram showed a large hyperechoic left kidney with poor corticomedullary demarcation, a small right kidney with severe loss of demarcation, thickened intestinal muscularis (up to 3.4 mm), and enlarged mesenteric lymph nodes (up to 6.4 mm). Cytology of the left kidney revealed large-cell lymphoma. Thoracic radiography was unremarkable, except for a prominent bronchial pattern. George is currently clinically well with a normal appetite.

CURRENT MEDICATION:

- 1) Dexamethasone 0.2 mg/kg IV q24h

FURTHER TESTING RECOMMENDED:

- 1) Feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) retroviral testing recommended. FeLV positive cats are associated with a poor prognosis (see further below under 'Prognosis'). FIV positive cats (which may be present in around 50% of cats with renal lymphoma) anecdotally have been associated with a higher risk of myelosuppression (particularly neutropenia) with chemotherapy. If cats are FIV positive, prophylactic antibiotics that are more effective against Gram-negative bacteria (pradofloxacin or marbofloxacin at 5mg/kg PO q24h) is recommended when starting any new myelosuppressive chemotherapy drug, until the neutrophil nadir is documented to be above 1.0.
- 2) There was mild monocytosis noted on haematology, which may be circulating lymphoma cells vs. normal reactive monocytes. Blood smear evaluation (if not already performed) is recommended to check for evidence of circulating lymphocytes. This will be useful in monitoring response to therapy.
- 3) Baseline urinalysis (and if indicated, urine culture and sensitivity) is recommended before starting chemotherapy, to rule out any subclinical urinary tract infections or other urinary abnormalities. If a urinary tract infection is present, it should be treated with appropriate antibiotics. It does not necessarily preclude treatment with chemotherapy. Urine specific

gravity is required before each treatment with doxorubicin. Doxorubicin can cause cumulative and irreversible renal toxicity in cats, even after doxorubicin has been discontinued. If there is underlying renal disease or the USG is <1.035, doxorubicin should be avoided and substituted with mitoxantrone. See further below under 'Comments.

CANCER BIOLOGY:

Lymphoma is the most common haematopoietic cancer in cats. The neoplasms usually arise in lymphoid tissues (such as lymph nodes, spleen, and bone marrow). However, they may arise in any tissue in the body.

There are several potential causes or risk factors for lymphoma in cats, including retroviral status (FeLV and FIV), genetic and molecular factors (oriental cat predisposed), environmental factors (exposure to environmental tobacco smoke), immunosuppression, chronic inflammation (inflammatory bowel disease) and diet.

Renal lymphoma is the second most common form of extranodal lymphoma in cats after nasal lymphoma. It can present confined to the kidneys or concurrently with alimentary or multicentric lymphoma. Around 40% of cats with renal lymphoma will have CNS involvement.

The median age of affected cats is nine years of age. However, renal lymphoma may occur in 6% of cats under one year of age. The majority of cats affected are not FeLV positive, but approximately half of the cats reported in Australia are FIV positive. The majority of cats with renal lymphoma have high-grade B cell lymphoma.

Cats with renal lymphoma typically present with signs consistent with renal insufficiency such as hyporexia, weight loss and PU/PD. Physical examination usually reveals palpable renomegaly (bilateral >80% cases). Ultrasonographic findings usually reveal bilateral, irregular and diffuse renomegaly with hypochoic subscapular thickening. This appears to be the case for George's left kidney.

PROGNOSIS:

Left untreated, the prognosis for high-grade lymphoma in cats is guarded with a median survival time of <2 months. Most cats are humanely euthanised due to poor quality of life.

The prognosis for lymphoma in cats is highly variable and depends on several factors, including:

1. Response to therapy.
 - The most important independent prognostic factor is achieving a complete remission with therapy. Cats that achieve a complete remission with chemotherapy have reported median survival times are between 8 months and 1.5 years, compared to 2 to 3 months in cats that did not achieve a complete remission (i.e. cats that achieved partial remission, stable disease or progressive disease).
2. Histologic grade.
 - The histologic grade of lymphoma is very important in prognosis. In cats with high-grade lymphoma, the median survival times with multiple agent chemotherapy is approximately 4 to 12 months. In contrast, cats with low-grade lymphoma have median survival times of

approximately two years with less aggressive therapy (i.e. oral chlorambucil and prednisolone therapy).

3. Large vs. small cell morphology.

- Cats with large cell lymphoma have a worse prognosis with a median survival time of approximately 1.5 months compared to 28 months in cats with small cell lymphoma.

4. FeLV status.

- FeLV is an important prognostic factor for feline lymphoma. FeLV positive lymphoma cats had a median survival time of approximately five weeks compared to 6 months in FeLV negative lymphoma cats. Also, FeLV positive cats that do not have an initial response to chemotherapy have shorter survival times.

5. Stage.

- Staging does not necessarily confer a worse prognosis, except for cats with stage I disease (i.e. single anatomical area or lymph node), which has a favourable prognosis. Several papers report a median survival time of approximately 1 to 1.5 years in cats with stage I nasal lymphoma treated with chemotherapy and/or radiation therapy.

6. Substage.

- Cats that present in clinical substage b (i.e. clinically unwell) had a better prognosis with a median survival time of approximately 3.5 months compared to 9.5 months if in clinical substage a (i.e. well). In particular, weight loss and anaemia have been associated with a worse prognosis.
- Weight loss at presentation confers a worse prognosis for achieving complete remission and survival.
- Weight gain during therapy in two studies was associated with a better prognosis. Cats with large cell lymphoma that lost $\geq 5\%$ of their body weight after one month of therapy had significantly shorter survival than those that gained or had a stable weight.
- In cats with nasal lymphoma, anaemia, anorexia and involvement of cribriform plate confer a worse prognosis.

7. Location.

- Location of lymphoma has also been shown to be prognostic.
- Cats with nasal lymphoma tend to respond better to therapy than lymphoma in other locations.
- Conversely, cats with renal lymphoma, tend to have a poorer prognosis.

8. Transmural vs. mucosal.

- Cats with histologically confirmed transmural involvement of their lymphoma had a worse prognosis with median survival times of approximately 1.5 to 3.5 months, compared to 29 months if lymphoma infiltrated the mucosal layer only.

9. Treatment type.

- Cats that receive doxorubicin in their chemotherapy protocol have a better prognosis than cats that do not receive doxorubicin. Doxorubicin, when used alone, has a response rate of

<30%. However, doxorubicin included in a COP based protocol, had median remission duration increased from approximately three months to 9.5 months.

10. Immunophenotype?

- Immunophenotyping for B and T cell lymphoma has not been extensively studied in cats. One study published just over two decades ago showed immunophenotyping was not prognostic in cats with lymphoma. Since then, many studies on feline lymphoma have not evaluated immunophenotyping. However, cats diagnosed with large or high-grade B cell lymphomas potentially may do better with therapy, than cats diagnosed with large-cell or high-grade T cell lymphomas.

11. Pre-treatment with steroids?

- Pre-treatment with steroids (e.g. prednisolone) may potentially be associated with a worse prognosis in cats with lymphoma. In one study, if cats achieve a complete remission to chemotherapy, pre-treatment with steroids before chemotherapy significantly reduced the survival. Median survival time was about eight months compared to about 1.5 years without prior steroid treatment. However, the response rate was not significantly different between pre-treatment prednisolone cats and those that were not pre-treated with steroids. When all cats were considered, pre-treatment steroids did not affect the response to treatment or survival.

George has renal lymphoma, which unfortunately has a worse prognosis than lymphomas in other locations. He also has presented with anaemia which is a negative prognostic factor. However, despite this, George is eating well, and his response to therapy is not yet known. If he can obtain complete remission, he has the potential to survive a long time with chemotherapy. The single most important independent prognostic factor is achieving a complete remission with therapy, and unfortunately, this will not be known until therapy is trialled.

TREATMENT OPTIONS:

Recommended treatment – multiple agent chemotherapy

The gold standard treatment of choice is multiple agent chemotherapy administered over a total period of approximately four months. Chemotherapy is administered via the intravenous, subcutaneous and/or oral route. Treatment usually consists of prednisolone concurrently with approximately four to five chemotherapy drugs (such as cyclophosphamide, l-asparaginase, vinblastine, doxorubicin ± procarbazine) rotated weekly for approximately three weeks, then every two weeks for the remaining duration of the protocol. The reported complete remission rate and median survival times with multiple agent chemotherapy for cats with renal lymphoma is approximately 50-70%, for approximately 3 to 6 months, respectively. Some cats are cured, living up to 2.5 years or longer. However, this is less likely (although not impossible) with renal lymphoma. Also, cats that achieve a complete remission with chemotherapy have reported median survival times between 8 months and 1.5 years, compared to 2 to 3 months in cats that did not achieve a complete remission (i.e. cats that achieved partial remission, stable disease or progressive disease).

Chemotherapy side effects are relatively uncommon occurring in approximately 10% of cats. Rarely do side effects result in hospitalisation.

For owners that have financial constraints, l-asparaginase can be omitted from the chemotherapy protocol. However, this will likely be less effective.

Alternative #1 – lomustine

Single-agent lomustine (CCNU) is a reasonable alternative and more cost-effective. Prednisolone is recommended concomitantly. CCNU is an oral alkylating agent administered every 5 to 6 weeks for approximately ten treatments, or for as long as it helps cats with lymphoma. A recent retrospective study evaluated 32 cats with treatment naïve intermediate to large cell gastrointestinal lymphoma (not renal lymphoma) treated with single-agent CCNU. Some cats received a single dose of l-asparaginase with the first CCNU treatment. The response rate (i.e. complete and partial remission) to CCNU was approximately 50%. Most cats had a clinical benefit from treatment. However, there were 30% of cats that did not respond to therapy. The median survival time for all cats in this study was 3.5 months. However, if cats achieved a complete remission with CCNU, the median survival time increased to 10 months. There is currently no survival data for the use of CCNU in cats with renal lymphoma. This is a less effective alternative if the owners cannot afford the recommended treatment option.

A complete blood count is required every seven days after the first CCNU treatment, for approximately 5 to 6 weeks. This is to establish the neutrophil nadir. However, some cats will not tolerate having a blood test performed each week. If George resents taking blood, CCNU may not be a good treatment option.

CCNU is tolerated well in cats. Chemotherapy side effects are relatively uncommon occurring in approximately 10% of cats. Rarely do side effects result in hospitalisation.

Alternative #2 – cyclophosphamide

Single-agent cyclophosphamide is also a reasonable and cost-effective alternative. Prednisolone is recommended concomitantly. Cyclophosphamide is an alkylating agent administered every 2-3 weeks in cats via the oral or intravenous route. Treatment is recommended for approximately ten treatments, or for as long as it helps cats with lymphoma. Two recent prospective studies confirmed that cyclophosphamide could be administered safely at higher dosages in tumour-bearing cats via both the intravenous and oral routes. Some cats received a single dose of L-asparaginase with the first cyclophosphamide treatment. Although there are no current studies to show a survival benefit at this higher dosage, I believe dosing cyclophosphamide in this way may benefit cats with lymphoma. There is currently no survival data for the use of cyclophosphamide in cats with renal lymphoma, but I have anecdotally had cats respond short-term to this therapy. Single-agent cyclophosphamide is a less effective alternative if the owners cannot afford the recommended treatment option.

Cyclophosphamide is tolerated well in cats. Chemotherapy side effects are relatively uncommon occurring in approximately 10% of cats. Rarely do side effects result in hospitalisation.

SUPPORTIVE CARE:

Single-agent prednisolone can clinically make cats feel better (and usually within 24-48 hours). However, it should not be used concurrently with non-steroidal anti-inflammatory drugs. In some instances, cats may achieve a complete remission with prednisolone alone. However, remission duration is often short-lived with reported median survival times of around 2 to 3 months. If the

owners elect to proceed with single-agent prednisolone, I recommend 40 mg/m² PO q24 hours for as long as it keeps George in remission.

Other supportive medications considered in cats (with or without chemotherapy) include antiemetics, appetite stimulants and anti-diarrhoeal medications, as required.

Chemotherapy can cause weight loss, which is associated with a worse prognosis, particularly if cats lose $\geq 5\%$ of their body weight after one month of therapy. These cats have significantly shorter survival than those that gained or have a stable weight.

In cats that are losing weight and not eating well, placement on an oesophagostomy tube may be necessary. Careful and repeated assessments of nutritional state, caloric intake, and body weight are required. Nutritional support is best instituted sooner rather than later. A good nutritional plan will help maintain or improve the cat's quality of life, immunologic status, and tolerance to chemotherapy.

SPECIFIC QUESTIONS:

- 1) Do cats require prophylactic antibiotics with chemotherapy treatment?
 - In cats undergoing chemotherapy, I do not usually recommend prophylactic antibiotics, except in cats that are FIV positive, have an underlying bone marrow disease, or evidence of neutropenia before starting chemotherapy. In those circumstances, prophylactic antibiotics that are more effective against Gram-negative bacteria (pradofloxacin or marbofloxacin at 5mg/kg PO q24h) is recommended for the first two weeks of starting any new myelosuppressive chemotherapy drug. Again, when the neutrophil nadir is $\geq 1.0 \times 10^9/L$, antibiotics can be discontinued, and there is no requirement for prophylactic antibiotics for subsequent treatments with that particular chemotherapy drug.

- 2) Do you think we should be giving darbepoetin to this cat? Or wait to see if the anaemia improves in response to the chemotherapy first?
 - If you are really concerned about the anaemia and the owners do not have financial constraints, I think darbepoetin short-term with chemotherapy is fine.
 - Alternatively, if the cat is clinically stable after the blood transfusion, you can start chemotherapy without darbepoetin, monitor PCV's closely and start darbepoetin when you are concerned.
 - I usually do not use darbepoetin because I think the underlying problem is the cancer. If you can control the cancer, the anaemia should improve slowly over time.

COMMENTS:

I have attached two multiple agent chemotherapy protocols for George (no additional charge). The first chemotherapy protocol (including doxorubicin), is my preference because cats that can receive doxorubicin have a more favourable survival outcome. However, George has underlying renal disease. Doxorubicin can cause cumulative and irreversible renal damage, therefore if his USG is not above 1.035 and his renal parameters not significantly improved by the time doxorubicin is due, please use the alternative protocol. Please also contact me if you would like another alternative protocol, particularly if you anticipate that the owners will have difficulties administering oral procarbazine chemotherapy at home.

The most important prognostic factor for cats with lymphoma is the cat's response to therapy. Therefore, repeat staging to assess remission status is crucial regularly. If the cat is clinically improved and doing well with treatment, I usually recommend repeat imaging approximately one to two months of initiating chemotherapy. However, if you are concerned, you can ultrasound the kidneys after each treatment. If there is evidence of progressive disease during therapy (i.e. failure to respond to therapy), the chance of further responses to chemotherapy is low with median survival times of approximately one month or less. At this point, therapy can be discontinued, or 'rescue' chemotherapy using drugs not present in the initial protocol considered. Conversely if the cat relapse after a long period of remission (e.g. more than six months after finishing chemotherapy), the cat has a high likelihood of attaining a second remission to chemotherapy, however, remission duration will probably be half that encountered in the initial therapy. Depending on when the cat relapses, a similar 're-induction' protocol may be recommended (\pm long-term maintenance therapy). Please contact The Pet Oncologist if you wish to discuss 'rescue' or 're-induction' chemotherapy options.

Before administering chemotherapy, it is crucial to be familiar with the specific drug handling, administration and storage requirements, potential side effects and safety of each chemotherapy drug. If required, chemotherapy drug information sheets can be provided by The Pet Oncologist (\$15 each or \$25 per protocol).

It is also vital to consider prophylactic antiemetics or other supportive care medications, particularly for owners where toxicity may result in discontinuing therapy. These supportive medications can be administered prophylactically when cats first start a new chemotherapy agent or started at the first signs of illness (e.g. nausea or vomiting). Occasionally cats will require dose reductions or treatment breaks in order to tolerate chemotherapy.

Lastly, to prevent the risk of gastrointestinal side effects and sepsis, cats receiving chemotherapy should only eat cooked foods (i.e. no raw meats or eggs).

DISCLAIMER:

This report is based on the medical information submitted and not on a physical examination of the patient. It has been prepared for interpretation by the licensed and registered veterinarian responsible for the care of this patient.

An invoice will be emailed to your nominated email for billings at the end of the month. Please kindly make payment within 7 days from the date of invoice.

Thank you! I hope this information is helpful. Please do not hesitate to contact me if you require clarification with this report or further assistance with this case.

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