

**Multicentric Lymphoma in the Dog:**  
*An Overview of Diagnostics, Treatment and Prognosis*  
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*This course provides an overview of the methods for diagnosing, treatment options and prognosis for dogs with lymphoma. This course includes a brief review of chemotherapy side effects and handling considerations in the veterinary clinic.*

## **Introduction**

Lymphoma is a general term used to describe cancers that arise from the lymphocytes. There are more than thirty different histologic subtypes of lymphoma described in the dog. The most common forms of lymphoma in the dog are intermediate to high grade, which means that they tend to be aggressive and spread rapidly in the body. The most common form of intermediate to high grade lymphoma in the dog is multicentric, meaning it involves all of the peripheral lymph nodes. Lymphoma may also be found in the liver or spleen, bone marrow or other organs including the central nervous system, kidneys, eyes, lungs or skin. Lymphomas can be further divided based on immunophenotyping – a test to determine if the cancer originates from B lymphocytes or T lymphocytes. Most intermediate to high grade lymphomas are B-cell lymphomas. B-cell lymphomas tend to respond better and longer to chemotherapy than T-cell lymphomas. Some lymphomas, particularly those of T-cell origin, cause hypercalcemia by releasing parathyroid hormone related peptide (PTHrP). Hypercalcemia causes additional clinical signs include polyuria/polydipsia, and, if left untreated, causes serious damage to the kidneys and other organs.

Multicentric lymphoma is commonly seen in middle aged to older, medium to large breed dogs. A higher incidence is reported in several breeds including Boxers, Bull Mastiffs, Basset Hounds, St. Bernards, Bulldogs, German Shepherd Dogs, Golden Retrievers, Labrador Retrievers and Rottweilers. Most dogs diagnosed with lymphoma have generalized, non-painful peripheral lymphadenomegaly. Most of these dogs will otherwise seem to be feeling fine and have no clinical signs related to their enlarged lymph nodes. When lymphoma does cause clinical signs, they are often non-specific and may include hyporexia, anorexia, weight loss, vomiting, diarrhea, polyuria, polydipsia, dyspnea, cavity effusion, and fever. While multicentric lymphoma (involving all of the peripheral lymph nodes) is the most common presentation, other anatomic forms exist and may result in clinical signs referable to the organ(s) involved (e.g., seizures or behavioral changes with CNS lymphoma, gastrointestinal disturbances with primary gastrointestinal lymphoma, skin or mucocutaneous lesions with epitheliotropic or cutaneous lymphomas and renal failure with renal lymphoma).

Lymphoma is a chemo-responsive tumor and dogs with lymphoma frequently achieve a complete remission following chemotherapy. The “gold standard” treatment for lymphoma is a multi-agent chemotherapy protocol called CHOP. Treatment with CHOP has a greater than 90% remission rate in dogs with B-cell lymphoma. Dogs with advanced disease at the time of diagnosis (e.g., bone marrow involvement or involvement of non-lymphoid organs), T-cell

lymphoma, anemia or clinical signs of illness at the time of diagnosis may not respond as well to treatment. Median survival time for dogs treated with CHOP is about 12 months. When lymphoma relapses, or the cancer recurs, the CHOP protocol can be repeated or there are many rescue chemotherapy protocols that can be used. Most dogs that are treated for lymphoma feel much better after starting therapy and enjoy good quality of life for up to a year or longer.

### **Diagnosing Lymphoma (Cytology vs. Histopathology)**

Arriving at a diagnosis of lymphoma is typically fairly straightforward. Fine needle aspirate (FNA) of an enlarged lymph node often provides the initial or presumptive diagnosis of the most common lymphomas. The mandibular lymph nodes are often reactive, so cytologic samples should target other lymph nodes if they are also enlarged (e.g., prescapular or popliteal lymph nodes). Histopathology of a lymph node biopsy is required to definitively diagnosis the grade of a lymphoma. Most intermediate to high grade lymphomas are very similar to Non-Hodgkin lymphomas (NHL) in people. As in people with NHL, diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of lymphoma in the dog.

While most lymphomas are intermediate to high grade, some lymphomas are indolent or low grade. These indolent or low grade lymphomas are best diagnosed via histopathology. Cytologic specimens from indolent or low grade lymphomas can be confusing and are often reported as reactive, hyperplastic or as emerging lymphoma. In some cases, cytologic samples from indolent lymphomas are reported as consistent with intermediate to high grade lymphoma. The long term prognosis for indolent or low grade lymphomas, such as T-zone lymphoma, is better than for intermediate to high grade lymphomas, such as DLBCL. Likewise the recommended treatment for indolent or low grade lymphomas (often chronic treatment with chlorambucil/Leukeran and prednisone) is typically different than that recommended for intermediate to high grade lymphomas (high dose, multi-agent chemotherapy protocols).

### **B-Cell vs. T-Cell**

In addition to grade, immunophenotype is prognostically significant for canine lymphomas. Most intermediate to high grade lymphomas are of B-cell origin, with most of the remainder being of T-cell origin. The adage, “B is better, T is terrible” reflects that B-cell lymphomas tend to respond better and for longer than T-cell lymphomas. B-cell lymphomas typically express the antigens CD79a, CD20 and PAX5. T-cell lymphomas typically express the antigen CD3. Immunophenotyping can be performed to detect these antigens via methods including immunohistochemistry (IHC) and immunocytochemistry (ICC). IHC is performed on formalin-fixed tissues and ICC is performed on cytologic specimens.

### **Molecular Testing (Flow Cytometry and PARR)**

In addition to IHC and ICC, complementary molecular testing such as flow cytometry and polymerase chain reaction for antigen receptor rearrangement (PARR) can document abnormalities within lymphoid populations. Flow cytometry is performed on liquid samples (blood, bone marrow or cytologic samples suspended in a mixture of 0.9% NaCl and canine serum) and provides information about the cell population present in a sample by separating the

cells using specific antibodies. Since antigen expression is different between T lymphocytes and B lymphocytes, this test is useful to describe the population of cells and suggest if neoplasia is present (e.g, a homogenous population of one type of lymphocyte is more likely to be lymphoma or leukemia than a heterogenous population of lymphocytes).

Unlike flow cytometry, PARR can be performed on either liquid samples or cytologic specimens that have been spread on a slide and stained. The PARR assay uses PCR to amplify and separate DNA from the T-cell receptor or B-cell immunoglobulin genes. This test is also referred to as a “clonality assay” because the results can determine if a monoclonal (cancerous) or polyclonal (reactive) population of T or B cells exists. The results of both flow cytometry and PARR are best interpreted in a pairwise fashion with cytologic or histopathologic evidence of neoplasia.

Due to the exquisite sensitivity of PCR, PARR can detect very low numbers of clonal cells and, while progression to visible lymphoma or leukemia is likely, some patients with a positive clonal PARR assay do not go on to develop cancer. In some cases in which a clonal lymphocyte population was detected, but there was no cytologic or histopathologic evidence of cancer, dogs were found to be positive for tick-borne diseases including *Ehrlichia canis*, Lyme disease, Bartonellosis and Rocky Mountain Spotted Fever. Flow cytometry and PARR are likely best used as complementary diagnostics for unusual or difficult cases of lymphoma/leukemia rather than as a means of routine diagnosis.

### Staging Tests

Staging is the collective term for a battery of tests performed to determine the extent of a tumor. Tumor stage (see Table 1) is prognostically significant for dogs with intermediate to high grade lymphoma. Complete staging would include complete blood count, chemistry panel (+/- iCa), urinalysis, three view thoracic radiographs, abdominal ultrasound (+/- abdominal radiographs, +/- FNA of the liver and spleen) and a bone marrow aspirate. Negative prognostic factors for lymphoma in the dog include stage IV or V disease, substage b disease, T-cell immunophenotype, presence of a mediastinal mass, anemia and prolonged pre-treatment with corticosteroids (due to upregulation of P-glycoprotein, which is implicated in chemotherapy resistance).

<i>Stage</i>		<i>Substage</i>	
<b>I</b>	Involves a <i>single lymph node</i> or <i>lymphoid tissue in a single organ</i>	<b>a</b>	No clinical signs related to the disease present ( <i>clinically well</i> )
<b>II</b>	Involves <i>regional lymph nodes</i> (typically confined to one side of the diaphragm)	<b>b</b>	Clinical signs related to the disease present ( <i>clinically ill</i> )
<b>III</b>	Generalized <i>lymph node involvement</i>		
<b>IV</b>	Involves the <i>liver or spleen</i>		

<b>V</b>	Involves the <i>bone marrow, blood or non-lymphoid organs</i> (e.g., eyes, brain, kidneys, skin, gastrointestinal tract, lungs, etc.)
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**Table 1. World Health Organization staging system for dogs with lymphoma.** Dogs with stage IV, stage V or substage (b) lymphoma are less likely to respond to chemotherapy and more likely to have a shorter response duration than dogs with lower stage disease (stage I, II or III) and no clinical signs of illness (substage a). Most dogs with lymphoma are stage III to IV and substage a.

## Hypercalcemia

Hypercalcemia is a well-documented paraneoplastic syndrome associated with lymphoma in the dog. Hypercalcemia is seen most often in T-cell lymphomas that secrete parathyroid hormone related peptide (PTHrP), resulting in an elevated ionized calcium. A so-called malignancy panel (ionized calcium, PTHrP and parathyroid hormone) is available, but the lag time between sample submission and availability of results may not be of clinical utility in most cases of lymphoma. Although total calcium is typically elevated in dogs with ionized hypercalcemia, it is possible to have an ionized hypercalcemia without a concurrent elevated total calcium. In cases where clinical signs of polyuria and polydipsia are present but a normal or borderline total calcium is present, checking ionized calcium is indicated.

## Initial Treatment

In most settings, chemotherapy is the treatment of choice for intermediate to high grade lymphoma in dogs. The most effective chemotherapy protocol is the CHOP chemotherapy protocol (see Table 2). This protocol utilizes three cytotoxic chemotherapy drugs (cyclophosphamide, doxorubicin and vincristine) in combination with prednisone. This protocol is often considered the “gold standard” for the treatment of lymphoma in dogs. Other treatment options include the COP chemotherapy protocol (cyclophosphamide, doxorubicin, vincristine and prednisone) or single-agent doxorubicin.

Cumulative treatment with doxorubicin may result in cardiotoxicity, so the COP protocol may be indicated in any dog with evidence of or a history of pre-existing heart disease. Evidence of pre-existing heart disease may include cardiomegaly, abnormal findings on an electrocardiogram or abnormal findings on an echocardiogram.

<b><i>UW-Madison 25 week CHOP Protocol</i></b>	
Week 1	CBC Vincristine 0.7 mg/m <sup>2</sup> or 0.5 mg/m <sup>2</sup> (if < 15 kg) IV bolus Prednisone 2 mg/kg PO SID
Week 2	CBC Cyclophosphamide 250 mg/m <sup>2</sup> IV bolus or PO Prednisone 1.5 mg/kg PO SID
Week 3	CBC Vincristine 0.7 mg/m <sup>2</sup> or 0.5 mg/m <sup>2</sup> (if < 15 kg) IV bolus Prednisone 1 mg/kg PO SID

Week 4	CBC, ECG Doxorubicin 30 mg/m <sup>2</sup> or 1 mg/kg (if < 15 kg) slow IV infusion (20 to 30 min) Prednisone 0.5 mg/kg PO SID
Week 5	CBC
Week 6	CBC Vincristine 0.7 mg/m <sup>2</sup> or 0.5 mg/m <sup>2</sup> (if < 15 kg) IV bolus
Week 7	CBC Cyclophosphamide 250 mg/m <sup>2</sup> IV bolus or PO Furosemide 1-2 mg/kg IV, IM or PO
Week 8	CBC Vincristine 0.7 mg/m <sup>2</sup> or 0.5 mg/m <sup>2</sup> (if < 15 kg) IV bolus
Week 9	CBC Doxorubicin 30 mg/m <sup>2</sup> or 1 mg/kg (if < 15 kg) slow IV infusion (20 to 30 min)
Week 11	CBC Vincristine 0.7 mg/m <sup>2</sup> or 0.5 mg/m <sup>2</sup> (if < 15 kg) IV bolus
Week 13	CBC Cyclophosphamide 250 mg/m <sup>2</sup> IV bolus or PO Furosemide 1-2 mg/kg IV, IM or PO
Week 15	CBC Vincristine 0.7 mg/m <sup>2</sup> or 0.5 mg/m <sup>2</sup> (if < 15 kg) IV bolus
Week 17	CBC Doxorubicin 30 mg/m <sup>2</sup> or 1 mg/kg (if < 15 kg) slow IV infusion (20 to 30 min)
Week 19	CBC Vincristine 0.7 mg/m <sup>2</sup> or 0.5 mg/m <sup>2</sup> (if < 15 kg) IV bolus
Week 21	CBC Cyclophosphamide 250 mg/m <sup>2</sup> IV bolus or PO Furosemide 1-2 mg/kg IV, IM or PO
Week 23	CBC Vincristine 0.7 mg/m <sup>2</sup> or 0.5 mg/m <sup>2</sup> (if < 15 kg) IV bolus
Week 25	CBC Doxorubicin 30 mg/m <sup>2</sup> or 1 mg/kg (if < 15 kg) slow IV infusion (20 to 30 min)

**Table 2. The CHOP chemotherapy protocol is considered the “gold standard” treatment for intermediate to high grade lymphoma in the dog.** A CBC is required before any dose of potentially myelosuppressive chemotherapy is administered. Chemotherapy should be delayed if the neutrophil count is <2,500/ul or the platelet count is <100,000/ul when treatment is due. Broad-spectrum antibiotics may be indicated if the neutrophil count is ≤1,000/ul. Febrile neutropenic dogs require immediate hospitalization for supportive care including intravenous fluids and broad-spectrum injectable antibiotics.

### Chemotherapy Side Effects

Chemotherapy is typically well tolerated in most dogs, but there is a risk for toxicity following treatment with any drug. Most chemotherapy drugs are capable of causing varying degrees of myelosuppression (typically manifest as neutropenia or thrombocytopenia), gastrointestinal disturbances (hyporexia, anorexia, nausea, vomiting, diarrhea or constipation) and alopecia (particularly in breeds with continually growing hair coats).

Most dogs will experience minimal side effects when treated with appropriate doses of chemotherapy and close monitoring. Some dogs will require supportive care in the form of anti-emetics, anti-diarrheals, dietary modification or prophylactic antibiotics. Rare dogs will have more serious side effects (typically due to severe neutropenia predisposing to the development of sepsis or severe gastrointestinal toxicity) that might require hospitalization for intravenous fluids and broad-spectrum antibiotics. Most dogs that experience significant chemotherapy related side effects can be successfully managed and resume their treatment protocols. Dose reductions and the prophylactic use of anti-emetics/anti-diarrheals are indicated in cases where dogs develop treatment-related side effects.

In addition to common chemotherapy side effects (myelosuppression, gastrointestinal disturbances and alopecia), drugs have varying capacities for unique toxicities (see Table 3) including cardiotoxicity (doxorubicin), hepatotoxicity (CCNU/lomustine), sterile hemorrhagic cystitis (caused by acrolein, an irritating metabolite of cyclophosphamide), paralytic ileus (vincristine) and hypersensitivity reactions (doxorubicin and L-asparaginase).

Many chemotherapy drugs are potent vesicants (blistering agents) and can cause extensive and severe tissue injury if they are extravasated. Of the common drugs used to treat lymphoma, doxorubicin, mechlorethamine, vincristine and vinblastine are considered vesicants. Chemotherapy drugs, and vesicant drugs in particular, are best administered through an intravenous catheter that is placed using a “one-stick” technique. Veterinarians administering chemotherapy should be familiar with the handling, storage, administration (route, rate and dilution, if needed) and toxicity of any chemotherapy drug given in their clinic.

<b>Chemotherapy Drug</b>	<b>Additional Toxicity of Note</b>
<i>Actinomycin-D (Cosmogen)</i>	Vesicant
<i>Cyclophosphamide (Cytoxan)</i>	Sterile hemorrhagic cystitis
<i>Doxorubicin (Adriamycin, hydroxydaunorubicin)</i>	Vesicant, cumulative dose-related cardiotoxicity, hypersensitivity reactions
<i>L-asparaginase (Elspar)</i>	Pancreatitis, hypersensitivity reactions
<i>CCNU (lomustine, CeeNU)</i>	Hepatotoxicity, pulmonary fibrosis
<i>Mechlorethamine (Mustargen)</i>	Vesicant
<i>Vinblastine (Velban)</i>	Vesicant
<i>Vincristine (Oncovin)</i>	Vesicant, paralytic ileus, peripheral neuropathy

**Table 3. Additional toxicity of note for selected chemotherapy drugs used to treat lymphoma in dogs.**

Virtually all cytotoxic chemotherapy drugs have the potential to cause myelosuppression (typically manifested as neutropenia or thrombocytopenia), alopecia (typically observed in dog breeds with constantly growing hair coats) and gastrointestinal upset (typically anorexia, nausea, vomiting or diarrhea). In addition to these generic chemotherapy side effects, many chemotherapy drugs have the potential to cause other drug-specific toxicity that are important to be aware of before using the drug.

### **MDR-1 Mutants and Chemotherapy**

A mutation in the gene for multi-drug resistance 1 protein (MDR-1), also known as P-glycoprotein 1 (Pgp) and ATP-binding cassette sub-family B member 1 (ABCB1), is commonly observed in Collies, Australian Shepherds and other herding breeds. The MDR-1 protein is a

cellular pump that removes drugs from inside of the cell. An MDR-1 mutation increases the toxicity of drugs like ivermectin, and may increase the severity of side effects from chemotherapy drugs including doxorubicin, vincristine and vinblastine. Prophylactic dose reductions (up to 50%) and supportive care (e.g., anti-emetics and anti-diarrheals) are indicated for dogs that harbor an MDR1 mutation.

Testing for MDR1 mutations is available through the Veterinary Clinical Pharmacology Laboratory at Washington State University (<https://vcpl.vetmed.wsu.edu/>).

### **Chemotherapy Safety for Clinic Staff**

Safety of the staff preparing and administering chemotherapy, and anyone else that could be exposed to drug residues in the clinic, is also a concern. Optimum equipment for the safe administration of chemotherapy include a class II biosafety cabinet (for chemotherapy drug preparation), N-95 respirators for all personnel during preparation and administration of chemotherapy, commercially available disposable chemotherapy-rated safety gowns and gloves, and a closed system transfer device (such as Equashield or Phaseal) for drug preparation and administration. Protective eyewear may be indicated for some chemotherapy drugs (e.g., mechlorethamine).

### **Chemotherapy Safety for Owners**

Owners giving oral chemotherapy drugs at home (such as cyclophosphamide or CCNU/lomustine) should be advised to handle the medications with care. Even though most oral chemotherapy drugs are supplied as coated tablets or capsules, latex or nitrile gloves should be worn to avoid accidental exposure to residues that may be present from manufacture or proximity to broken tablets or capsules. Chemotherapy pills and tablets should never be split, crushed or dissolved or handled by children under the age of 18 years, women who are or may become pregnant, women who are lactating or immunosuppressed individuals in the household. Standard methods used to tempt dogs to take pills can be employed (e.g., hiding the pills in a small snack) if needed, but care should be taken to avoid breaking open or dissolving capsules and tablets.

Chemotherapy residues may persist in bodily fluids, particularly urine and feces, following treatment, but would be expected to be highest in the 48 to 72 hours following administration. Similar handling precautions (latex or nitrile gloves) should be employed for bodily fluids, including urine, feces and vomitus, from pets that have recently been treated with chemotherapy. Drug residues in the environment are likely inactivated with time, but other pets should be discouraged from consuming feces of animals that are being treated with chemotherapy. For bodily fluids in the home, care should be taken to avoid aerosolizing liquids (e.g., blot the area with paper towels that have been sprayed with a cleaning solution rather than spraying a cleaning solution directly on to a liquid). Any potentially contaminated materials should be doubled bagged and disposed of in the household trash.

## **Prognosis**

For the most common form of intermediate to high grade lymphoma (DLBCL), treatment with the CHOP chemotherapy protocol typically results in a complete remission (all lymph nodes return to normal size and any clinical signs that are present resolve) in up to 95% of patients. The median survival time following treatment with CHOP is approximately 12 months.

Approximately 20% of dogs diagnosed with lymphoma will live longer than 2 years. Patients with the negative prognostic factors mentioned previously (stage IV or V disease, substage b disease, T-cell immunophenotype, presence of a mediastinal mass, anemia and prolonged pre-treatment with corticosteroids) are less likely to achieve a complete remission and more likely to have a shorter remission duration.

Up to 90% of dogs treated with the COP chemotherapy protocol achieve a complete remission and a median survival time of approximately 10 months. As a primary treatment, single agent doxorubicin (typically in combination with a 4 week tapering course of prednisone) can result in a complete remission in up to 75% of patients and a median survival time of up to 8 months.

## **Relapse and Rescue Chemotherapy**

While most lymphomas respond to chemotherapy and most dogs achieve a complete remission, relapse eventually occurs in most patients. In dogs treated with the CHOP chemotherapy that develop a durable remission (e.g., those that achieve a complete remission and finish the initial CHOP protocol), restarting CHOP at the time of the first relapse is typically recommended. Since the cumulative lifetime dose of doxorubicin is limited to 150-180 mg/m<sup>2</sup>, most dogs that are treated with a second CHOP chemotherapy protocol have mitoxantrone substituted for doxorubicin after the cumulative fifth dose of doxorubicin has been administered. Up to 90% of dogs that relapse after finishing CHOP and are treated with a second CHOP protocol will achieve a complete remission. In these cases, the second remission duration is typically shorter than the first.

If a dog fails CHOP before completing the first protocol (e.g., a dog's lymph nodes begin to increase in size before finishing the protocol) or fails during the second protocol, other rescue chemotherapy protocols are often initiated. Rescue chemotherapy is typically initiated and then continued until relapse – most dogs that start rescue chemotherapy will continue to receive rescue chemotherapy for the remainder of their life. Rescue chemotherapy protocols are less likely to result in a complete remission and some dogs will only achieve a partial remission (a significant decrease in their lymph node size, but not a complete return to normal) or stable disease (no reduction in their lymph node size, but also no growth). The drugs used in rescue chemotherapy protocols typically work by different mechanisms than the drugs used in the CHOP chemotherapy protocol in an attempt to circumvent chemotherapy resistance.

The most frequently used rescue protocols for relapsed lymphoma include LAP (L-asparaginase, lomustine/CCNU, and prednisone) and MOPP (mechlorethamine, vincristine, procarbazine and prednisone). These rescue protocols typically result in the best tumor response and are generally well tolerated. Mechlorethamine was originally derived from mustard gas and residual drug in vials and syringes must be neutralized with sodium thiosulfate following administration. Due to

the additional handling and safety issues associated with administration of mechlorethamine, the MOPP chemotherapy protocol is typically administered by veterinary oncologists with access to a class II biosafety cabinet. These protocols can result in a response (complete remission, partial remission or stable disease) in up to 70% of patients with a typical duration of 2 to 3 months.

Other rescue protocols for lymphoma include single-agent dacarbazine (DTIC), DMAC (dexamethasone, melphalan, actinomycin-D and cytosine arabinoside) and vinblastine. These protocols are generally associated with lower response rates, lower response durations and more severe treatment-related toxicity (particularly DMAC, which often causes severe thrombocytopenia).

## References

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*For information on flow cytometry and PARR, visit the Colorado State University College of Veterinary Medicine Clinical Immunology Laboratory website at <http://csu-cvmb.colostate.edu/academics/mip/ci-lab/Pages/default.aspx>.*

*For information on MDR1 testing, visit the Washington State University College of Veterinary Medicine Veterinary Clinical Pharmacology Lab website at <https://vcpl.vetmed.wsu.edu/>.*

## QUIZ

1. Which of the following is not a negative prognostic indicator for intermediate to high grade lymphoma in the dog?
  - a. B-cell immunophenotype
  - b. Stage IV
  - c. Substage b
  - d. Anemia
2. Most dogs diagnosed with lymphoma are presented to a veterinary clinic for evaluation of generalized non-painful peripheral lymphadenomegaly.
  - a. True
  - b. False
3. Which of the following antigens is found on T-cell lymphomas and can be detected using immunohistochemistry?
  - a. CD79a
  - b. CD20
  - c. PAX-5
  - d. CD3
4. Most dogs with intermediate to high grade lymphoma will achieve a complete remission when treated with the CHOP chemotherapy protocol.
  - a. True
  - b. False
5. The median survival time for a dog with multicentric B-cell lymphoma treated with the CHOP chemotherapy protocol is approximately \_\_\_\_\_.
  - a. 9 months
  - b. 12 months
  - c. 18 months
  - d. 24 months
6. Which of the following chemotherapy drugs may be more toxic in a dog that harbors an MDR-1 mutation?
  - a. CCNU (lomustine, CeeNU)
  - b. Cyclophosphamide (Cytoxan)
  - c. Dacarbazine (DTIC)
  - d. Vincristine (Oncovin)

7. Cardiotoxicity is a cumulative toxicity of which of the following drugs used to treat intermediate to high grade lymphoma?
  - a. Cyclophosphamide (Cytosan)
  - b. Doxorubicin (Adriamycin, hydroxydaunorubicin)
  - c. Mechlorethamine (Mustargen)
  - d. Vincristine (Oncovin)
  
8. Sterile hemorrhagic cystitis is a toxicity associated with which of the following drugs used to treat intermediate to high grade lymphoma?
  - a. Cyclophosphamide (Cytosan)
  - b. Doxorubicin (Adriamycin, hydroxydaunorubicin)
  - c. Mechlorethamine (Mustargen)
  - d. Vincristine (Oncovin)
  
9. Which of the following personal protective equipment should be utilized when handling, preparing or administering chemotherapy drugs?
  - a. N-95 respirator
  - b. Chemotherapy gloves and gowns
  - c. A closed system transfer device (e.g., PhaSeal, Equashield)
  - d. All of the above
  
10. Which of the following individuals should not handle an oral chemotherapy drug at home?
  - a. A child under the age of 18 years
  - b. A pregnant woman
  - c. A person that is being treated with immunosuppressive drugs
  - d. All of the above