Rescue Treatment of Canine Lymphoma

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Chemotherapy is the choice of treatment for multicentric lymphoma, approximately 70% to 95% of the cases achieve remission, period in which the patients do not present signs of disease, and because in most of the cases chemotherapy is well tolerated, a good quality of life is maintained during the remission time. Many protocols have been developed for the treatment of canine lymphoma, but independently of the protocol used, eventually, the majority of the patients will present loss of remission in approximately 6 to 9 months after the treatment is initiated. This period may vary between few weeks to years after initiated. In the majority of the cases, a remission can be achieved again in one or more additional times when rescue protocols are used. After a second or third loss of remission, the rate of dogs that achieve a new remission decreases in each consequent cycle. This resistance may be present because of the emergence of tumor cells that are more inherently resistant to chemotherapy. Many rescue protocols for canine lymphoma are described in the literature, but there is not much information about which rescue protocol and the order that the rescue protocols have to be used once the loss of remission is present. Many factors have to be considered for the selection of the protocol, such as the clinical status of the patient, clinical presentation of the disease, previous protocol used, previous response to the treatment, side effects to previous drugs, owner expectatives, cost, time interval between treatments, drug availability in the geographic area, clinical experience with the protocol and knowledge about possible modifications in the protocol, such as increment or decrement of doses, adding, subtracting or substituting drugs; This causes that an individual selection has to be done for each case and the order will not be the same in the majority of the cases. The recommendations that can be useful in the selection of a rescue protocol in my experience are:

Dogs initially treated with COP protocol for induction (combination protocol with cyclophosphamide, vincristine and prednisone) or COAP (same as COP plus cytosine arabinoside) for a period of 8 weeks, are followed with LMP protocol for maintenance (methotrexate, chlorambucil and prednisone) for the period where the remission time is sustained. When the patients did not achieve a complete remission at the end of the induction of the COAP protocol or when a loss of remission happens during the LMP, generally the addition of vincristine every two weeks to the LMP protocol in a dose of 0.5 mg/m² alternated with the chlorambucil is enough to reinduce and maintain a remission. If the remission is not achieved, the dose is increased to 0.75 mg/m². With the addition of vincristine to the LMP protocol, many cases achieve a long second remission time, but when a second loss of remission is present or if the increment in the vincristine dose was not enough to maintain the remission, a rescue protocol has to be started.

In dogs initially treated with an induction protocol containing doxorubicin (for example the Wisconsin-Madison 19 weeks protocol) and if the patient is in complete remission when the protocol is finished, no maintenance therapy is given. Once the loss of remission is present, the protocol is reinitiated again for 19 weeks. Caution with doxorubicin is advised, because during the second cycle, the maximum accumulative dose is achieved and the substitute of doxorubicin with actinomycin-D or mitoxantrone is recommended. When a
second period of complete remission is achieved, generally the LMP protocol with or without vincristine is given. In cases where a second remission is not obtained, a second loss of remission is present or when the patients did not respond to the first induction, a rescue protocol without doxorubicin is started.

Asparaginase as a single agent induces in the majority of the cases a complete remission, but because this time is usually short, the administration of other chemotherapy agents is needed. Before starting a rescue protocol, the administration of asparaginase can be indicated with the goal of obtaining a better response; because the effect of the asparaginase is usually limited only to the first two to three administrations, its use is recommended when it’s believed to be really necessary (eg. If a complete remission is achieved when a rescue protocol is started, the dose of the asparaginase may be “saved” for the future, but if only a partial remission is obtained, intensification with asparaginase may be necessary). The asparaginase is contraindicated in dogs predisposed to present pancreatitis.

Rescue protocols:

DMAC protocol.

In a study of 25 cases of canine lymphoma, actinomycin D was used as a single agent for rescue treatment and no response was noted in any case. But in my experience, actinomycin D combined with other drugs as in DMAC protocol, a complete remission can be achieved in approximately 80% of the cases after the first relapse; also this protocol has a lower toxicity in comparison with protocols containing doxorubicin and the patients need to visit the veterinarian every 15 days. If a remission is obtained, the protocol is continued for 6 to 8 cycles and then an LMP protocol for maintenance (with or without vincristine) is used until the loss of remission is detected.

CHOP protocol.

Another option is the administration of a CHOP protocol when a poor response is achieved with a DMAC protocol. If a complete response is achieved with the CHOP protocol, this is continued for 4 cycles and then a LMP protocol with vincristine or cytosine arabinoside (in alternated weeks with the chlorambucil) for maintenance is recommended.

Lomustine

With the use of lomustine as a rescue protocol, a response is expected in 30% of the cases with a response period of 3 months approximately. Its efficacy can be improved with the administration of asparaginase before lomustine is started. Usually the lomustine is given in combination with prednisone. A side effect to be considered is that the lomustine can cause hepatotoxicity in some cases. In a study with 43 dogs with resistant lymphoma, a response was noted in 27% of the cases and a complete remission in 7% of the cases with a median duration time of response of 86 days.

ADIC protocol

In a study with 15 dogs with relapsed lymphoma treated with the ADIC protocol, which contains doxorubicin and dacarbazine, a complete remission was observed in 33% of the cases with a median duration time of less than 42 days.

Doxorubicin

A reinduction of remission with doxorubicin as a single agent is a protocol that presents the advantage of being administered every 3 weeks, but because of its cardiotoxicity, it
has a maximum accumulative dose of 180 to 240 mg/m². Therefore, it is not recommended to be used for more than 6 to 8 doses and is contraindicated in dogs previously diagnosed with dilated cardiomyopathy. In a study with 12 dogs with relapsed lymphoma treated with doxorubicin as a single agent, a complete remission was achieved in 33% of the cases with a median duration time of 152 days. Oral cyclophosphamide can be added in a dose of 100 mg/m² in day 10 and 11 after doxorubicin (AC protocol).

**MOPP protocol**

In one study with 17 dogs treated with the MOPP protocol (meclorhethamine, vincristine, procarbazine y prednisone) after failing other protocols, a general response was achieved in 88% of the cases and a complete remission in 35% of the cases with a duration response of 28 days.

**Mitoxantrone**

Mitoxantrone is given in a dose of 6 mg/m² every 21 days. In one study with 15 dogs with loss of remission, a complete response was achieved in 47% of the cases with a median duration time of 84 days.

**INDUCTION PROTOCOLS**

**COAP protocol**

<table>
<thead>
<tr>
<th>Week</th>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vincristine</td>
<td>0.5 mg/m² IV</td>
</tr>
<tr>
<td></td>
<td>Cytosine arabinoside</td>
<td>300 mg/m² SQ divided in 2 to 4 doses every 12 hrs</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide*</td>
<td>50 mg/m² PO every 48 hrs for 8 weeks.</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
<td>40 - 50 mg/m² PO SID 7 days, Then 20 a 25 mg/m² EOD for 8 weeks.</td>
</tr>
<tr>
<td>2</td>
<td>Vincristine</td>
<td>0.5 mg/m² IV</td>
</tr>
<tr>
<td>3</td>
<td>Vincristine</td>
<td>0.5 mg/m² IV</td>
</tr>
<tr>
<td>4</td>
<td>Vincristine</td>
<td>0.5 mg/m² IV</td>
</tr>
<tr>
<td>5</td>
<td>Vincristine</td>
<td>0.5 mg/m² IV</td>
</tr>
<tr>
<td>6</td>
<td>Vincristine</td>
<td>0.5 mg/m² IV</td>
</tr>
<tr>
<td>7</td>
<td>Vincristine</td>
<td>0.5 mg/m² IV</td>
</tr>
<tr>
<td>8</td>
<td>Vincristine</td>
<td>0.5 mg/m² IV</td>
</tr>
<tr>
<td></td>
<td>*Substitute with chlorambucil 20 mg/m² PO every 15 days, if hemorrhagic cystitis is developed.</td>
<td></td>
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</tbody>
</table>

**Wisconsin Madison-19 (WM-19) protocol**

<table>
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<th>Drug</th>
<th>Dose</th>
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<tr>
<td>1</td>
<td>L-asparaginase</td>
<td>400 UI/kg IM</td>
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<tr>
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<td>Vincristine</td>
<td>0.5 a 0.7 mg/m² IV</td>
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<tr>
<td></td>
<td>Prednisone</td>
<td>2 mg/kg PO SID</td>
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<tr>
<td>2</td>
<td>Cyclophosphamide*</td>
<td>200 to 250 mg/m² IV</td>
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<tr>
<td></td>
<td>Prednisone</td>
<td>1.5 mg/kg PO SID</td>
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<tr>
<td>3</td>
<td>Vincristine</td>
<td>0.5 a 0.7 mg/m² IV</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
<td>1 mg/kg PO SID</td>
</tr>
<tr>
<td>4</td>
<td>Doxorubicin**</td>
<td>30 mg/m² IV</td>
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<tr>
<td></td>
<td>Prednisone</td>
<td>0.5 mg/kg PO SID</td>
</tr>
<tr>
<td>5</td>
<td>Vincristine</td>
<td>0.5 a 0.7 mg/m² IV</td>
</tr>
<tr>
<td>6</td>
<td>Cyclophosphamide</td>
<td>200 a 250 mg/m² IV</td>
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<tr>
<td>7</td>
<td>Vincristine</td>
<td>0.5 a 0.7 mg/m² IV</td>
</tr>
<tr>
<td>8</td>
<td>Doxorubicin</td>
<td>30 mg/m² IV</td>
</tr>
</tbody>
</table>
MAINTEINANCE PROTOCOL

LMP protocol

- Chlorambucil 20 mg/m² PO every 15 days.
- Methotrexate 2.5 to 5 mg/m² PO twice a week.
- Prednisone 20 mg/m² PO EOD

When vincristine is added a dose of 0.5 a 0.7 mg/m² IV is given every 15 days alternating weeks with the chlorambucil.

RESCUE PROTOCOLS

DMAC protocol

- Actinomycin-D 0.75 mg/m² IV on day 1.
- Cytosine arabinoside 300 mg/m² SQ on day 1.
- Dexamethasone 0.5 mg/lb PO on days 1 and 8.
- Melphalan 20 mg/m² PO on day 8**

*El ciclo es repetido cada 15 días

**The melphalan is substituted with chlorambucil 20 mg/m² after 3 to 4 cycles.

CHOP protocol

- Doxorubicin 30 mg/m² IV on day 1 (1 mg/kg in dogs under 15 kg).
- Vincristine 0.7 mg/m² IV on days 7 and 15.
- Cyclophosphamide 200 mg/m² PO on day 10.
- Prednisone 20 mg/m² PO EOD.
- Sulfathiazole 15 mg/kg every 12 hrs PO.

*The cycle is repeated every 21 days.

If a complete remission is achieved, no maintenance protocol is given and the protocol is reinitated when loss of remission is seen.

* Substitute with Chlorambucil 20 mg/m² PO every 15 days, if hemorrhagic cystitis is developed.

** Doxorubicin in dogs <15 kg, use a dose of 1 mg/kg
Lomustine

Lomustine 60-80 mg/m² PO every 21 days
Prednisone 40-50 mg/m² EOD for 7 days, then 20-25 mg/m² EOD.

Protocolo ADIC

Doxorubicin 30 mg/m² IV on day 1 (1 mg/kg in dogs under 15 kg).
Dacarbazine 700 a 1000 mg/m² IV by infusion for 6 to 8 hrs on day 1
*The cycle is repeated every 21 days.

Suggested readings


