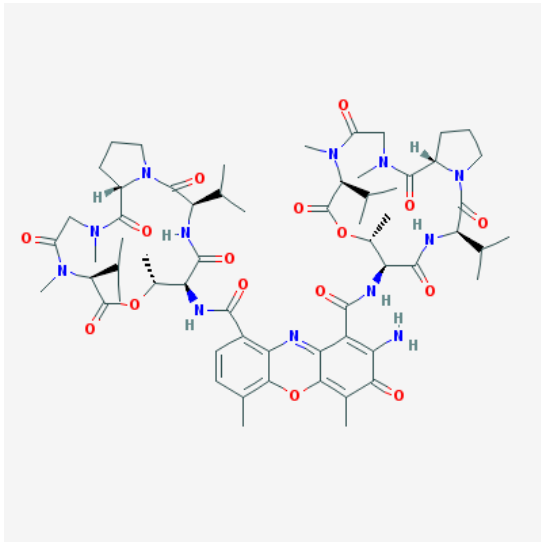


## KEY POINTS:

1. Dactinomycin (Actinomycin D®, Cosmegen®) has been reported as an effective treatment in dogs with relapsed or chemotherapy-resistant lymphoma when used as either a single agent or in combination with other chemotherapy drugs and protocols<sup>1-3</sup>.
2. Dactinomycin has been reported to be effective as a first-line treatment in the management of dogs with lymphoma<sup>4</sup>.
3. The most commonly reported dosage used in dogs is 0.5-1.0 mg/m<sup>2</sup><sup>2,3,5</sup>.
4. Some adverse effects reported with the use of dactinomycin are thrombocytopenia<sup>1,2,5</sup>, myelosuppression<sup>2</sup>, neutropenia<sup>2,4</sup>, gastrointestinal toxicity<sup>3,4,5</sup>, anorexia<sup>3</sup>, vomiting<sup>3</sup>, and diarrhea<sup>3,5</sup>.
5. Dactinomycin has been shown to be effective in the management of canine malignancies in single or multi-agent chemotherapy protocols<sup>1-4</sup>.

## BACKGROUND: WHAT IS DACTINOMYCIN?



**Figure 1.** Dactinomycin is a compound composed of a two cyclic peptides attached to a phenoxazine<sup>6,7</sup>.

Dactinomycin is a chromopeptide antineoplastic antibiotic isolated from the bacterium *Streptomyces parvulus*. Dactinomycin intercalates between adjacent guanine-cytosine base pairs blocking the transcription of DNA by RNA polymerase; it also causes single-strand DNA breaks, possibly via a free-radical intermediate or an interaction with topoisomerase II<sup>6</sup>.

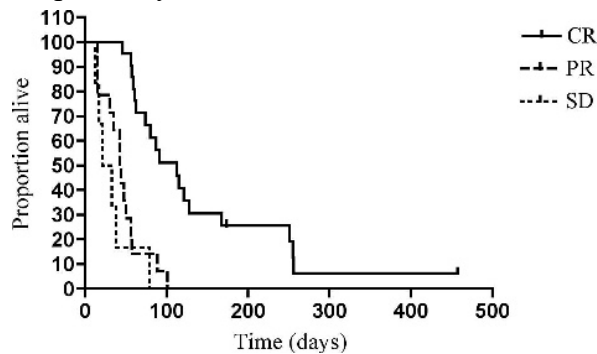
Dactinomycin is a chemotherapy drug that has been reported useful as a treatment for resistant or relapsed lymphoma in dogs<sup>1-3</sup>; but Dactinomycin has also been shown as an effective treatment for newly diagnosed lymphosarcomas in dogs<sup>4</sup>. Dactinomycin is poorly absorbed; therefore, it must be given intravenously<sup>5</sup>.

### **STUDY 1: DACTINOMYCIN, IN COMBINATION WITH OTHER CHEMOTHERAPY, HAS BEEN REPORTED HELPFUL IN MANAGING DOGS WITH RESISTANT OR RELAPSED LYMPHOMA<sup>1</sup>**

In this retrospective study, the response of 54 dogs either having relapsed or having chemotherapy-resistant lymphoma to a combination chemotherapy protocol using

dexamethasone, melphalan, Actinomycin D<sup>®</sup>, and cytosine arabinoside (DMAC Protocol) was reported.

- Dogs were given a median of 3 cycles of DMAC treatment.
- The overall response rate to DMAC was reported as 72%, with 44% of dogs having a complete response (CR), 28% of dogs having a partial response (PR), and 11% having a stable response (SD).
- The median remission times for the CR, PR, and SD groups were 112, 44, and 27 days respectively.



**Figure 2.** Duration of remission in 41 dogs who achieved CR (n=21), PR (n=14), and SD (n=6) treated with DMAC (P=0.0001). The median remission duration for dogs with CR, 112 days (range, 26–467+ days); PR, 44 days (range, 15–89 days); and SD, 27 days (range, 13–79 days)

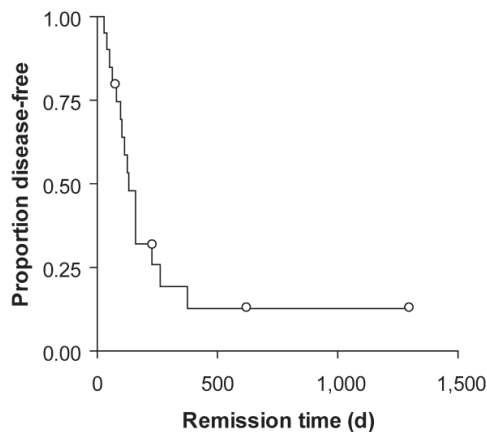
- A major factor that affected the inability to achieve remission in the dog was previous treatment doxorubicin.
- Adverse events reported included thrombocytopenia (56% of dogs), neutropenia (17% of dogs), and gastrointestinal toxicoses (22% of dogs).
- Adverse events were associated with greater severity in dogs having prior exposure to lomustine chemotherapy or when DMAC was used as a second, third, or fourth rescue protocol.
- Based on the study results, the DMAC protocol is an effective rescue protocol for dogs with resistant lymphoma.

## **STUDY 2. SINGLE-AGENT USE OF DACTINOMYCIN HAS BEEN REPORTED EFFECTIVE IN THE MANAGEMENT OF DOGS WITH RELAPSED OR RESISTANT LYMPHOMA <sup>2</sup>**

In this retrospective study, 49 dogs with relapsed lymphoma or showing resistance to other chemotherapy drugs were treated with single-agent Actinomycin D<sup>®</sup>.

- Dogs received a median intravenous dosage of 0.68 mg/m<sup>2</sup> (0.46–0.72 mg/m<sup>2</sup>) for 1 to 7 treatments (median, n=1).

- 20 of 49 (41%) dogs had a CR following Actinomycin D<sup>®</sup> treatment.



**Figure 3.** Kaplan-Meier curve of disease-free interval for 20 dogs with relapsed or resistant lymphoma that had a complete remission following administration of actinomycin D as a single agent for rescue chemotherapy. Open circles represent censored cases.

- The median disease-free interval for 16 of the 20 dogs having a CR was 129 days (range, 42-1293 days). The other 4 dogs having a CR were not considered because they were alive at the time of analysis.
- Concurrent prednisone administration, number of previous chemotherapy drugs received, and duration of first remission were significantly correlated with a response to Actinomycin D<sup>®</sup>.
- Thrombocytopenia was the most common adverse effect in this study. Thrombocytopenia was identified in 22 of the 49 (45%) dogs.
- Based on the results of this study, Actinomycin D<sup>®</sup> is effective for dogs with relapsed or resistant lymphoma when used as single agent chemotherapy treatment.

### STUDY 3: DACTINOMYCIN IS REPORTED USEFUL IN THE MANAGEMENT OF CANINE MALIGNANCIES <sup>3</sup>

In this prospective study, 50 dogs with various malignancies were treated with Actinomycin D<sup>®</sup> every three weeks.

- Dogs were treated with a dose of Actinomycin D<sup>®</sup> ranging from 0.5 to 1.1 mg/m<sup>2</sup>.
- The median number of treatment cycles of Actinomycin D<sup>®</sup> was 2 (range, 1-8 treatments).
- Of the 50 dogs enrolled in this study, 8 dogs died from progressive disease before the first week of chemotherapy, 4 dogs were lost to follow-up after the initial administration, and 4 dogs were incorrectly entered in the study.
- Of the 34 dogs evaluated for response to treatment, 12 had lymphoma (36%), 16 had carcinomas (47%), 2 had sarcomas (6%), 3 had melanomas (8%), and 1 had mesothelioma (3%).
  - In the 12 dogs with lymphoma, 5 had a CR and 5 had a PR to Actinomycin D<sup>®</sup> treatment (overall response rate, 83%). Nine of these dogs had prior chemotherapy and 7 of them responded to Actinomycin D<sup>®</sup> treatment (78%).
  - Of the other malignancies, there were 6 dogs having a PR to Actinomycin D<sup>®</sup> treatment; anal sac adenocarcinoma (n=1), squamous cell carcinoma (n=1),

thyroid carcinoma (n=1), perianal adenocarcinoma (n=2), and transitional cell carcinoma (n=1).

- The most common side effect reported was gastrointestinal usually presenting as vomiting and/or diarrhea, observed in 15 of the 45 dogs. Hematologic toxicity was reported in 2 dogs.
- Based on the results of this study, Actinomycin D<sup>®</sup> may offer an alternative to other broad-spectrum chemotherapeutic agents; however, it is most effective as a treatment for lymphoma.

#### **STUDY 4: RANDOMIZED CONTROLLED TRIAL REPORTING DACTINOMYCIN AS AN EFFECTIVE TREATMENT IN DOGS WITH MALIGNANT LYMPHOMA<sup>4</sup>**

In this prospective study, 21 dogs with malignant lymphoma were treated with a multiagent protocol including Dactinomycin.

- Dogs were included in the study if no previous chemotherapy agents had been administered.
- Results measured were time to first remission, duration of first remission, survival time, and prevalence of toxicoses. The resultant mean dose for Dactinomycin was 0.72 mg/m<sup>2</sup> with only 2 dogs given one dose, and the rest receiving multiple doses.
- Four (4) dogs died before the first dose of Dactinomycin could be administered do to disease or disease related complications, and 1 withdrew from the study.
- The 16 dogs remaining were given Dactinomycin, and 14 (67%) achieved CR, 1 (5%) achieved PR.
  - Time to first remission in dogs that received Dactinomycin was an average of 20 days (12-29). The duration of first remission was 154 days (106-226), and median survival time was 236 days (197-439).
- There were 11 episodes of dose-limiting neutropenia in 7 dogs, with only 6 of the 11 cases being related to the administration of Dactinomycin. One dog died from complications from neutropenia and sepsis. One dog developed dose limiting gastrointestinal toxicoses.
- Based on the results of this study Dactinomycin, when used in combination with other agents, may be useful in the treatment of dogs with lymphoma.

#### **CONCLUSIONS:**

Dactinomycin has been shown to be an effective treatment in the management of canine malignancies in single or multi-agent chemotherapy protocols. Highest response rates have been observed in dogs with relapsed or resistant lymphoma. Adverse effects have been reported following treatment and may be more pronounced in dogs receiving prior chemotherapy agents

(Doxorubicin). Adverse events may include thrombocytopenia, neutropenia, gastrointestinal toxicity, anorexia, vomiting, and diarrhea.

### **HOW SUPPLIED:**

Dactinomycin for Injection USP is a lyophilized soluble powder. In the dry form the compound is an amorphous yellow to orange powder. The solution is clear, gold-colored and essentially free from visible particles. This drug is highly toxic and both powder and solution must be handled with caution and administered with care. Reconstitute Dactinomycin by adding 1.1 mL of Sterile Water for Injection (without preservative) using aseptic technique. The resulting solution of Dactinomycin will contain approximately 500 mcg (0.5 mg) per mL.<sup>8</sup>

<sup>1</sup> Alvarez F.J. et al. (2006) Dexamethasone, melphalan, actinomycin D, cytosine arabinoside (DMAC) protocol for dogs with relapsed lymphoma. *J Vet Intern Med.*, 20(5), 1178-83.

<sup>2</sup> Bannink E.O. et al. (2008). Actinomycin D as rescue therapy in dogs with relapsed or resistant lymphoma: 49 cases (1999--2006). *JAVMA*, 233(8), 446-51.

<sup>3</sup> Hammer A.S. et al. (1994). Treatment of tumor-bearing dogs with actinomycin D. *J Vet Intern Med.*, 8(3), 236-9.

<sup>4</sup> Khanna C. et al. (1998) Randomized controlled trial of doxorubicin versus dactinomycin in a multiagent protocol for treatment of dogs with malignant lymphoma. *J Am Vet Med Assoc.*, 213(7), 985-90.

<sup>5</sup> Plumb, D.C. (2015) Dactinomycin. *Plumbs Veterinary Handbook* (8<sup>th</sup> Edition).

<sup>6</sup> *National Cancer Institute's Drug Thesaurus*. Dactinomycin (Code C412). Version 16.05e.

<sup>7</sup> National Center for Biotechnology Information. PubChem Compound Database; CID=457193.

<sup>8</sup> "Dactinomycin Injection." Dactinomycin Injection - FDA Prescribing Information, Side Effects and Uses. Bedford Laboratories, Aug. 2012. Web.