

Original Research Article

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Adverse Effects of Chemotherapy with Doxorubicin and Vincristine in Canine Transmissible Venereal Tumour

Anup Yadav¹, Praveen Kumar^{2*}, Lokesh³, Ashwani Kumar², Pankaj Kumar⁴,
Rajendra Yadav⁵, N.S. Bugalia¹ and R.P. Diwakar⁶

¹Department of Veterinary Gynaecology and Obstetrics, ²Department of Veterinary Medicine, ³Department of Veterinary Surgery, (LUVAS, Hisar), India

⁴Disease Investigation Laboratory, Rohtak (LUVAS, Hisar), India

⁵RVDEC, Mahendergarh (LUVAS, Hisar), India

⁶Department of Veterinary Microbiology, C.V.Sc&A.H., N.D.U.A&T., Kumarganj, Faizabad (U.P), India

*Corresponding author

ABSTRACT

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Present study was conducted at TVCC, LUVAS, Hisar on Twenty-four dogs irrespective of age, breed, sex affected with canine transmissible venereal tumour (TVT). Affected dogs were divided equally into three groups on the basis of treatment with chemotherapeutic drugs viz. vincristine therapy (Group I) and doxorubicin therapy (Group II and III). Vomition, diarrhea, alopecia, allergic nodules and stomatitis were adverse effects of chemotherapy in TVT affected dogs. Maximum adverse effects of chemotherapy were recorded with vincristine therapy (Group I), followed by 14 days interval doxorubicin therapy (Group II) and minimum adverse effects with 21 days interval doxorubicin (Group III).

Introduction

Canine transmissible venereal tumour (TVT) is a benign reticulo endothelial tumour of the dog that mainly affects the external genitalia and this tumor contradicts the current view that cancer cells generate more mutations and inevitably become more aggressive if untreated. Naturally occurring TVT occurs in dogs, with no breed or sex predilection (Rogers *et al.*, 1997; Murgia *et*

al., 2006). TVT incidence has been reported in several areas around the world. However, it has mostly been found in tropical and subtropical urban areas with a large random mating population of free-roaming dogs with poor mating control (Das *et al.*, 2000, Mello *et al.*, 2005, Rogers *et al.*, 1998). Tumor is spread by transplantation of tumor cells from the affected area to the mucous membrane, particularly to membranes that have lost their integrity.

Sexual intercourse is major route of transmission of TVT. However, other social behaviors of dogs, such as licking and sniffing, are also able to promote the transmission of TVT (Papazoglou *et al.*, 2001). Chemotherapy is the most effective and practical therapy, with vincristine sulfate being the most frequently used drug (Calvet *et al.*, 1982). Vincristine, used as a chemotherapeutic agent, is a plant alkaloid and is widely used to treat various neoplastic disorders, such as, leukemias, lymphomas and sarcomas in dogs and cats (Dobson *et al.*, 2008, Hahn, 1990]. This alkaloid disrupts cellular microtubule formation and exerts cytotoxic activity. This leads to inhibition of cell replication, including the replication of the cancer cells (Copocc, 2009). The TVT treatment by vincristine consist of weekly administration of at a dosage of 0.5 to 0.7 mg/m² of body surface area or 0.025mg/kg b. wt. for a period of 4–8 weeks (Boscos *et al.*, 2004]. There are various other chemotherapeutic agents like cyclophosphamide, vinblastine and methotrexate, which have been used alone or in combination in treatment regimen. However, there is no apparent advantage in the combination of chemotherapy over using vincristine alone (Richardson, 1981, Johnston, 1991., Brown *et al.*, 1981; Yang *et al.*, 1991).

Resistant cases of drugs viz. vincristine sulphate, vinblastine, cyclophosphamide, and methotrexate can be treated with doxorubicin (Richardson., 1981; Souza *et al.*, 1998). Doxorubicin is the anthracycline and antitumour antibiotic family of medications. It works in part by interfering with the replication of DNA (Tacar *et al.*, 2013). When total regression of the tumor cannot be achieved by chemotherapy, either electrocauterization or cryocauterization (Vermooten, 1987 and Rogers., 1997) or radiotherapy (Vermooten, 1987; McEvoy, 1987; Rogers, 1997 and Boscos and Ververidis, 2004) or surgical management

(Prier and Johnson, 1964; Jackson, 1969; Weir *et al.*, 1987; Johnson,1994; Bradley, 1996; Rogers, 1997; Boscos and Ververidis, 2004) or immunotherapy (Amber *et al.*, 1990 and Powers, 1968 and Rogers., 1997) or biotherapy (Richardson, 1981; Amber *et al.*, 1990 and Johnston, 1991) are adopted.. In cases that fail to resolve with chemotherapy, radiotherapy has been reported to yield good results (Das *et al.*, 2000).

Major advantages of chemotherapy are the high cure rate, ease of administration and potential usefulness in metastatic and multifocal disease. The disadvantages of chemotherapy are due to adverse effects observed during and after treatment e.g. loss of appetite, vomition, diarrhoea, neutropenia, alopecia, paresis etc. Behavioural changes are also observed during chemotherapy like animal feels lonely, occupies dark corner in the house and does not guard the house (Gadmada, 2006, Gandotra *et al.*, 1993, Gandhimathi *et al.*, 2011).

Materials and Methods

Experimental animals

Male and female dogs selected for the present study were client-owned clinical cases those were brought to the Teaching Veterinary Clinical Complex, LUVAS, Hisar for treatment purpose. Twenty-four dogs (male and female) affected with transmissible venereal tumour constituted into three experimental groups (8 animals in each group).

Experimental design

In present investigation, diagnosis of TVT and its therapeutic management was done. Diagnosis of TVT in dogs was made on the basis of clinical history given by owner followed by clinical examination and confirmed by histopathological examination

of biopsy tissue. Variations in haematological and biochemical parameters in canine TVT were also recorded. Therapeutic efficacy of three different treatment regimens was evaluated and compared on the basis of regression of tumor as recorded by post-treatment clinical examinations conducted on days 7 to day 14 post-treatment (Group I), days 14 to day 28 post-treatment (Group II) and days 21 to day 42 post-treatment (Group III) or up to full regression of tumor.

Experimental groups

A total of twenty-four male and female dogs with the clinical history of bleeding from penis, prepuce and cauliflower like growth on base of penis in males and vaginal bleeding and cauliflower like growth in vagina in females following mating were divided equally into three groups each comprising of eight dogs irrespective of sex.

Group I (n=8): Male and female dogs were treated with Vincristine sulphate @ 0.025 mg/kg b. wt., IV at weekly interval. The vincristine was administered on Day 0, Day 7 and Day 14

Group II (n=8): Male and female dogs were treated with Doxorubicin Hydrochloride @ 30mg/m² [Surface area= Body weight^{0.67} X K/10⁴ - Sandhu and Rampal (2006)] IV in 100ml NSS. The Doxorubicin was administered on Day 0, Day 14 and Day 28

Group III (n=8): Male and female dogs were treated with Doxorubicin Hydrochloride @30mg/m² IV in 100ml NSS. The Doxorubicin was administered on Day 0, Day 21 and Day 42.

Diagnosis

Dogs (both male and female) suspected for the TVT were diagnosed on the basis of

clinical history recorded from owners and confirmed by histopathological examination of biopsy tissue of tumour mass. In addition haematological and biochemical parameters were monitored.

Procedure for clinical examination and adverse effect of drugs

TVT's were examined per vaginum in female dogs and by backward retraction of prepuce in male dogs and confirmed by the presence of cauliflower like tumour mass on the base of penis and vagina. The tumors were examined for shape, size, location and presence of bleeding associated with them. Adverse effects like vomition, diarrhoea, alopecia, stomatitis, allergic nodules of chemotherapy treated dogs affected with TVT were also recorded in affected dogs.

Results and Discussion

Adverse effects of chemotherapy in canine TVT

Adverse effects of cytotoxic drugs recorded in TVT affected male and female dogs (Group I, Group II and Group III) (Table 1).

Vomition and diarrhoea

Vomition and diarrhoea were observed in 5 out of 8 dogs and 4 out of 8 dogs respectively in vincristine regimen (Group I). Similar adverse effect with vincristine was recorded by Amber *et al.*, (1990); Gandotraet *al.*, (1993) and Gandhimathi *et al.*, (2011).

Vomition and diarrhoea were observed in 4 out of 8 dogs and 2 out of 8 dogs respectively in doxorubicin regimen (Group II) and 2 out of 8 dogs showed both adverse effects in doxorubicin regimen (Group III). Similar adverse effect with doxorubicin was recorded by Talker, (2001); Gadmade, (2006) and Gandhimathi *et al.*, (2011).

Vomition after cytotoxic drug administration is consequential to drug induced damage of gastro-intestinal epithelium, liver, kidney and brain (Dobson and Gorman, 1993) and can be minimized following fluid therapy and antiemetics (Gandotra *et al.*, 1993).

Morrison (1998) reported that the non-specific epithelial cells damage of the intestine results in malabsorption resulting in diarrhoea, whereas Dobson and Gorman (1993) reported that the direct cytotoxic action of the drug on the rapidly dividing cells of the oral basal epithelial, gastric mucosa and intestinal crypt epithelium might result in gastrointestinal toxicity. It may also occur as a result of non-specific immunosuppression . Rehydration therapy along with antimicrobial therapy and supportive therapy was instituted that helped in speedy recovery in most of the affected cases.

Alopecia

Alopecia was recorded in 2 out of 8 dogs after vincristine therapy (Group I). Similarly, alopecia was recorded after vincristine chemotherapy in canine TVT (Amber *et al.*, 1990, Gandotra *et al.*, 1993 and Gandhimathi *et al.*, 2011).

Only one out of 8 dogs showed alopecia after doxorubicin treatment regimen (Group II). None of the dogs showed alopecia following

doxorubicin treatment regimen (Group III). Alopecia increased during course of chemotherapy and dog recovered from alopecia after 4-5 week after chemotherapy. Morrison (1998) also reported that alopecia was not observed after Doxorubicin chemotherapy and present observation are in concurrence with this report.

Dobson and Gorman (1993) reported silky or curly coat breeds to be affected with alopecia. Recorded alopecia in TVT dogs with chemotherapy could be due to cutaneous toxicity.

Stomatitis

Stomatitis was observed in one dog in each group (vincristine- Group I and doxorubicin-Group III) and could be attributed to individual sensitivity of dog to chemotherapy.

Allergic nodules

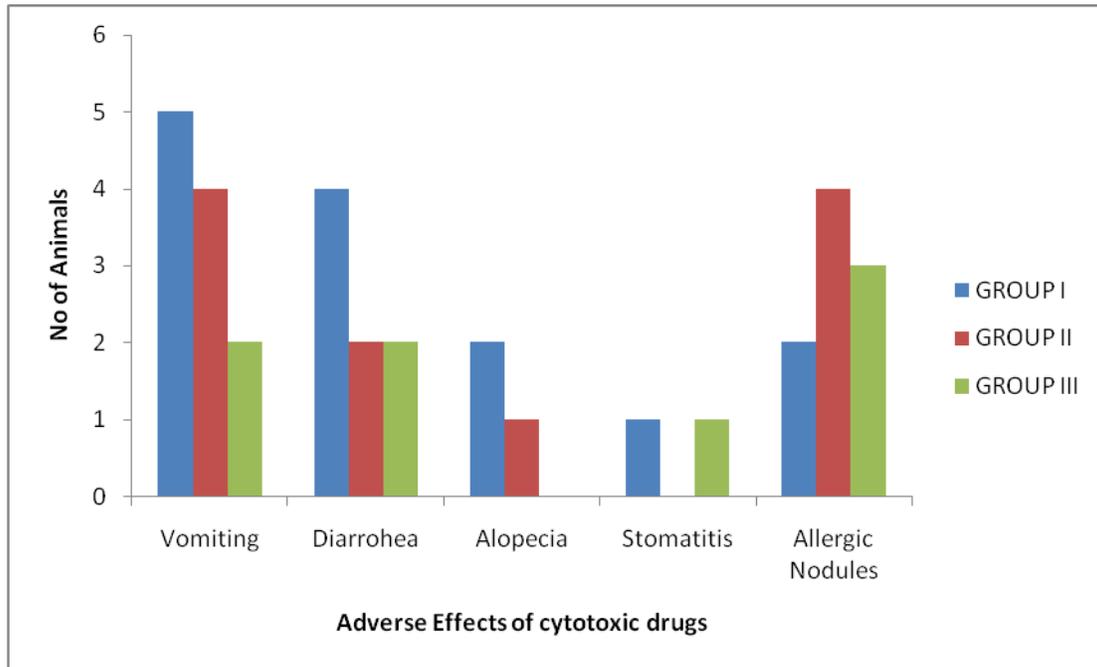
Allergic nodules were recorded in 2 out of 8 dogs in vincristine treatment regimen (Group I), 4 out of 8 dogs in doxorubicin treatment regimen (Group II) and 3 out of 8 dogs (37 %) in doxorubicin treatment regimen (Group III).

Allergic nodules observed during course of chemotherapy subsided following avil therapy for three consecutive days (Fig. 1).

Table.1 Adverse effects of chemotherapy in canine TVT

Clinical Signs	GROUP I (n=8)	GROUP II (n=8)	GROUP III (n=8)
Vomiting	5	4	2
Diarrhoea	4	2	2
Alopecia	2	1	-
Stomatitis	1	-	1
Allergic Nodules	2	4	3

Fig.1 Histogram showing adverse effects of cytotoxic drugs in TVT affected male and female dogs (Group I, Group II and Group III)



It is concluded as vomiting and Diarrhoea were most common and alopecia and allergic nodules were less common adverse effects with vincristine chemotherapy (Group I). Vomiting and allergic nodules were most common and diarrhea and alopecia were less common with doxorubicin chemotherapy (Group II). Allergic nodules were most common and vomiting, diarrhea and stomatitis were less common adverse effects with doxorubicin chemotherapy (Group III). Maximum adverse effects of chemotherapy were recorded with vincristine therapy (Group I), followed by 14 days interval doxorubicin therapy (Group II) and minimum adverse effects with 21 days interval doxorubicin therapy (Group III).

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