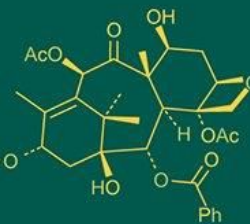
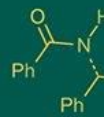


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Effect of Cisplatin chemotherapy in peri anal tumours affected dogs

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Abstract

The objective of the present study was to evaluate the therapeutic efficacy of Inj. Cisplatin in the treatment of peri anal tumors. Dogs that were presented to the Veterinary Clinical Complex for a period of two years were screened for the presence of peri anal tumors. The clinical recovery, hematological and biochemical parameters and the therapeutic efficacy of treatment were enumerated.

Keywords: Perianal tumors, dogs, Cisplatin, therapeutic efficacy, clinical recovery

Introduction

Perianal (hepatoid) glands are specialized sebaceous glands found in the skin surrounding the anus, foreskin, tail base, groin, and inner thighs of dogs. These glands are prone to neoplastic transformations, with the most common type of tumor form being adenoma. In male dogs, tumors affecting the anal region are a significant health concern, ranking as the third most common type of tumor after skin and testicular cancers. According to studies, perianal tumors account for approximately 9-18% of all skin cancers in male dogs (Bray, 2011) [5]. Various treatment options have been explored for managing these tumors. The present study aims to evaluate the effectiveness of cisplatin chemotherapy in treating perianal tumors in dogs.

Materials and Methods

The dogs presented to clinic and those referred from various hospitals in and around Hyderabad to Teaching Veterinary Clinical Complex, Bhoiguda formed the basis for the present study. Whole blood and serum samples of all the selected dogs formed the clinical material for laboratory examination. Clinical samples for hematology and biochemistry i.e., blood and sera samples were collected from all the dogs with malignancy for laboratory examination. In dogs with malignancy, blood and sera samples were collected before therapy. Blood and serum were also collected from apparently healthy dogs to establish normal values. Two ml of whole blood was withdrawn from cephalic or saphenous vein in vacutainer with KEDTA for estimation of hematological parameters. For separation of serum, 5 ml of blood was collected in a vacutainer containing clot accelerator. Serum was separated immediately after clotting by centrifugation at 3000 rpm for 5 minutes and collected in ependorff tubes. Care was taken during collection and processing of blood samples to avoid haemolysis. Serum samples were collected for the estimation of biochemical parameters. Estimation of all the hematological and biochemical parameters was carried out on the same day of collection. However, blood was also collected from apparently healthy dogs to establish normal values.

Hematology

Hematological parameters such as Hb, PCV, TEC, TLC and DLC were estimated as per the standard procedures. Hemoglobin was estimated by Sahli's comparator method and the concentration was expressed as g/dl. Packed cell volume was estimated by microhematocrit method and values were expressed as per cent. Total erythrocyte count was examined by haemocytometer and the results were expressed as number of erythrocytes x 10⁶ per microliter of blood. Total leucocyte count was examined by haemocytometer and the results were expressed as number of leucocytes x10³ per microliter of blood.

Blood smears were prepared on a clean grease free slide and stained by Leishman's stain for DLC. Cells were counted by battlement method and expressed as percentage.

Serum biochemistry

All the serum biochemical parameters were estimated by semi auto analyzer (Star 21 plus, supplied by M/s Rapid Diagnostics, New Delhi) employing the kits supplied by Span diagnostics Pvt. Ltd.

Alanine aminotransferase (ALT): Serum ALT was estimated by kinetic assay method and the values were expressed as IU/L.

Aspartate Aminotransferase (AST): Serum AST was estimated by kinetic assay method and the values were expressed as IU/L.

Alkaline Phosphatase (ALP): Serum ALP was estimated by kinetic assay method and the values were expressed as IU/L.

Total Protein: Total Protein was estimated by end point method (Modified Biuret) and the values were expressed as g/dl.

BUN: BUN was estimated by initial rate assay (NED-dye) and the values were expressed in mg/dl. Creatinine: Creatinine was estimated by initial rate assay (Modified Jaffe's reaction) and the values were expressed in mg/dl.

Group VII dogs were treated with Cisplatin (Inj. Platinex) @ 50 mg/m² mixed with Normal saline and administered i/v once in a week for a maximum of 5 doses

Results

Clinical improvement

Clinical signs reported in affected dogs were shown in table 1 and histopathological types of canine peri anal tumours were shown in table 2. In peri anal tumours affected dogs, 10 dogs were taken up for therapy with Inj. Platinex 7 dogs showed reduction in tumour size by day 21 (i.e. week days after 3rd dose) and partial response (PR) was seen by day 35 (i.e. 7 days after the 5th dose) while no response of tumour size was noticed in 3 dogs even after 5th dose of Inj. Platinex administration until 3 months after completion of chemotherapy. (Plate No. 22). In the present study

chemotherapy with Inj Platinex showed partial response (PR) of the tumour size. 7 out of 10 dogs showed partial response (PR) of tumour i.e 70% of the dogs responded for the treatment but incompletely, rest of the 3 (30%) dogs showed stable disease/ no change (NC) of the mass. In affected dogs, out of the 7 dogs which showed partial response the other clinical signs were also relieved to a greater extent and the symptoms persisted in the three dogs which did not respond.

Hematological findings

Haematological examination of affected dogs before during and after therapy revealed that the mean Hb, PCV, TEC had significantly declined ($p < 0.01$) from day 0 to day 35. Leucopenia was significant during therapy ($p < 0.01$) and until day 35. Neutrophilia was significant ($p < 0.05$) on day 0 when compared to that of apparently healthy dogs and mean neutrophil count significantly declined ($p < 0.01$) during therapy until day 35 (one week after therapy). Significant lymphocytosis ($p < 0.01$) was seen during the course of therapy. Monocytes and eosinophils did not show any significant alterations. During therapy, thrombocytopenia was significant till day 35 ($p < 0.01$) (Table 3).

Table 1: Clinical signs seen in Perianal tumour affected dogs (No.=41)

Sl. No	Clinical sign	No of dogs	Percent
1	Masses in Perianal region	41	100
	Solitary nodules	18	43.90
	Multiple nodules	23	56.10
2	Dyschezia	35	85.37
3	Tenesmus and constipation	23	56.10
4	Discomfort	16	39.02
5	Hematochezia	15	36.59
6	Ulceration and licking	13	31.71
7	Anorexia	10	24.39
8	Weight loss and lethargy	9	21.95
9	Polydipsia and polyuria	8	19.51

Table 2: Histopathological types of canine perianal tumours (No.=41)

S. No.	Type of tumour	No. of Dogs	Percentage
1	Hepatoid Adenocarcinomas	24	58.54
2	Myxosarcoma	9	21.95
3	Squamous cell carcinoma	5	12.20
4	Fibro haemangiosarcoma	3	7.31
	Total	41	100

Table 3: Mean haematological values of dogs in Group I (Apparently Healthy) and Group II (Perianal tumours) before, during and after therapy

S. No.	Parameter	Group I Apparently Healthy dogs (n=10)	Group II dogs Before therapy (n=10)	Group II Dogs During and After therapy (n=10)				
				0day	7 th day	14 th day	21 st day	28 th day
1	Haemoglobin (g/dl)	13.75±0.51	12.96±0.88	12.13±0.2	10.57±1.11	9.25±1.2 ^{##}	7.94±1.09 ^{##}	7.44±1.2 ^{##}
2	PCV%	41.60±0.91	39.14±1.26	36.40±0.54	31.71±0.56	27.76±0.48 ^{##}	23.82±0.48 ^{##}	22.54±0.52 ^{##}
3	TEC (x 10 ⁶ /μl)	6.63±0.3	6.52±1.08	6.06±0.02	5.78±0.02	4.62±0.01 ^{##}	3.97±0.02 ^{##}	3.82±0.01 ^{##}
4	TLC (x 10 ³ /μl)	13.30±0.86	16.82±1.01*	14.38±0.1	11.32±0.19	10.42±0.1	10.12±0.11	9.47±1.12 ^{##}
5	DLC (%)							
	Neutrophils (%)	72.0±0.32	75.03±0.42*	69.85±0.91	64.86±0.4	59.82±0.36	54.53±0.3	51.92±1.35 ^{##}
	Lymphocytes (%)	24.0±0.14	20.05±0.25*	25.08±0.60	30.09±0.80	35.03±0.78	41.08±0.90	43.05±2.18 ^{##}
	Monocytes (%)	2.00±0.36	2.27±0.52	2.48±0.62	2.85±0.51	2.50±0.42	2.24±0.89	2.69±0.48
	Eosinophils (%)	2.00±0.80	2.65±0.28	2.59±0.36	2.20±0.34	2.65±0.30	2.15±0.20	2.34±0.30
6	Platelets (x 10 ⁵ /dl)	3.06±0.24	3.11±0.2	1.92±0.01	2.10±0.02	1.42±0.04	1.61±0.02	1.28±0.03 ^{##}

** : Significant at $p < 0.01$ when compared to apparently healthy dogs; * : Significant at $p < 0.05$ when compared to apparently healthy dogs ##

: Significant at $p < 0.01$ when compared to before therapy; # : Significant at $p < 0.05$ when compared to before therapy

Table 4: Mean serum biochemistry of dogs in Apparently Healthy and Perianal tumours before, during and after therapy

S. No.	Parameter	Group I Apparently Healthy dogs (n=10)	Group II dogs Before therapy (n=10)	Group II Dogs During and After therapy (n=10)				
			0 day	7 th day	14 th day	21 st day	28 th day	35 th day
1	BUN (mg/dl)	16.29±0.44	17.74±1.57	24.12±0.62	30.58±0.91	37.00±0.52	43.42±0.64	49.84±2.4 ^{##}
2	Creatinine (mg/dl)	0.95±0.62	1.02±0.03	1.27±0.02	1.53±0.03	1.78±1.01	2.04±1.03	2.29±1.03 ^{##}
3	ALT (IU/L)	30.47±0.98	38.04±1.1*	47.43±0.1	51.63±0.1	55.82±0.1	60.01±0.1	64.21±1.1 ^{##}
4	AST (IU/L)	39.86±0.36	39.94±0.2	45.23±0.2	50.53±0.2	55.82±0.2	61.12±0.2	66.41±0.2 ^{##}
5	ALP (IU/L)	42.90±0.80	45.12±2.3	55.75±0.3	66.38±2.3	77.01±0.3	87.64±0.01	98.27±0.02 ^{##}
6	Total Protein (g/dl)	6.70±0.14	6.46±0.74	6.28±0.01	6.10±0.02	5.92±1.22	5.74±1.26	5.56±0.98 ^{##}

** : Significant at $p<0.01$ when compared to apparently healthy dogs; * : Significant at $p<0.05$ when compared to apparently healthy dogs
 ## : Significant at $p<0.01$ when compared to before therapy; # : Significant at $p<0.05$ when compared to before therapy

Biochemical changes

The dogs affected with perianal tumours showed a significant increase ($p<0.01$) in the mean post therapeutic levels of BUN, creatinine, ALT, AST and ALP when compared to pre-therapeutic means. However a significant decline ($p<0.01$) in total protein level was noticed post therapeutically when compared to pretherapeutic mean. (Table 4)

Discussion

In 10 dogs of affected dogs taken up for therapy with Inj. Cisplatin 7 dogs showed reduction in tumour size by day 21 (i.e.7 days after 3rd dose) and partial response was seen by day 35 (i.e.7 days after 5th dose) while no response of tumour size was noticed in 3 dogs even after 5th dose of Inj. Cisplatin. 7 dogs out of 10 dogs showed partial response i.e., 70% of the dogs responded for the treatment but partially, rest of the 3 (30%) dogs were showing stable disease / no change (NC) of the mass. In affected dogs out of the 7 dogs which showed partial response the other clinical signs were also relieved to a greater extent and the symptoms persisted in those which did not respond. Similar findings were reported by Bennett *et al.* (2002) [3] who reported that partial response was seen in 4 out of 13 dogs treated with Inj. Cisplatin indicating the role of platinum chemotherapeutic drugs in dogs with perianal tumours. They also reported that the platinum drugs had anti tumour activity and as perianal tumours progress slowly in some patients, it was not possible to know if the stable disease with chemotherapy was truly a drug effect or simply a reflection of slow tumour progression.

Haematological examination of peri anal tumour affected dogs before during and after therapy revealed that the mean Hb, PCV, TEC had significantly declined ($p<0.01$) from day 0 to day 35. Leucopenia was significant during therapy ($p<0.01$) and until day 35. Neutrophilia was significant ($p<0.05$) on day 0 when compared to that of apparently healthy dogs and mean neutrophil count significantly declined ($p<0.01$) during therapy until day 35 (one week after therapy). Significant lymphocytosis ($p<0.01$) was seen during the course of therapy. Monocytes and eosinophils did not show any significant alterations. During therapy, thrombocytopenia was significant till day 35 ($p<0.01$). Similar findings were reported by Bennett *et al.* (2002) [3] and Barabos *et al.* (2008) [2] who stated that myelosuppression was the reason for decrease in the haematological parameters which may be associated with the death of the rapidly dividing cells in the bone marrow.

In dogs affected with perianal tumours showed a significant increase ($p<0.01$) in the mean post therapeutic levels of BUN, creatinine, ALT, AST and ALP when compared to pre-therapeutic means. BUN and creatinine were showing

alarming increase during the course of therapy. BUN increase may be linked to decreased glomerular filtration rate or increase protein catabolism caused by necrosis of tumour or metabolic side effects of neoplasia. The cytotoxic drugs got deposited in bone marrow and were detoxified by liver because of that liver was loaded much for secretion of liver enzymes. This overload lead to the increase of ALT, AST and ALP values during therapy. However a significant decline ($p<0.01$) in total protein level was noticed post therapeutically when compared to pre-therapeutic mean. Similar findings of nephrotoxicity were reported by Bennett *et al.* (2002) [3] and Barabas *et al.* (2008) [2] who stated that the morphological alterations in the kidney attributed to Inj. Cisplatin administration occur in the pars recta of the proximal tubule situated in the outer stripe of the medulla. One of the earliest of histopathological changes noted were the swelling of mitochondria and pathological changes mostly start by 3 days after Inj. Cisplatin administration including clumping nuclear chromatin, increased number of cytoplasmic vesicles, focal loss of microvillus brush border and completely sloughing of necrotic cells in the tubular lumen. Banerjee *et al.* (2018) [4] reported that dogs received cisplatin adjuvant chemotherapy Anal Sac Gland Carcinoma showed more favourable prognosis than surgery alone. The standard treatment for anal gland tumours was chemo - radiation with a combination of fluoropyrimidines and Cisplatin. (Francesca *et al.* 2019) [6]. Cytotoxic chemotherapy drugs such cisplatin, have been recommended following initial surgical resection (Repasy *et al.* 2022) [8].

Side affects

On the other hand treatment side effects of Inj. Cisplatin included profuse vomiting, diarrhoea and anorexia. These side effects started in 8 dogs from day 14 (one week after 2nd dose) slowly and aggravated in these dogs by day 21. All the dogs were administered supportive treatment for these side effects and the treatment was continued uninterruptedly. Similar observations were made by Natasa *et al.* (2005) [7] and Bennett *et al.* (2002) [3] who stated that mild gastrointestinal adverse effects were seen in 25% of cases treated with Inj. Cisplatin and Barabas *et al.* (2008) [2] who stated that gastrointestinal toxicity and myelosuppression were seen in Inj. Cisplatin treatment which may be associated with the death of the rapidly dividing cells lining the gastrointestinal tract and in the bone marrow. Inj. Cisplatin also activates the chemoreceptor trigger zone to induce vomiting.

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