Journal of Entomology and Zoology Studies

Available online at www.entomoljournal.com

E-ISSN: 2320-7078
P-ISSN: 2349-6800
JEZS 2018; 6(2): 2934-2936

Received: 13-01-2018
Accepted: 14-02-2018

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Cisplatin-based adjuvant chemotherapy in dogs with anal sac gland carcinoma

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Abstract
Canine Anal Sac Gland Carcinoma is an uncommon skin neoplasm and highly invasive in character. The present study was conducted to find out whether adjuvant therapy of cisplatin would more effective than surgery alone in Canine Anal Sac Gland Carcinoma(ASGC). 30 pet dogs with naturally occurring ASGC were included in this study. The present study demonstrated that dogs received cisplatin adjuvant therapy have significantly less serum calcium level (X^2 =4.83 P<0.05), metastasis rate(X^2 =5.75 P<0.05). and local recurrence rate (X^2 =5.19 P<0.05) than dogs had surgery alone. This study also revealed that cisplatin adjuvant therapy also significantly prolonged survival time in dogs (10.74 ± 0.35, P<0.05). In conclusion our result suggest that dogs received cisplatin adjuvant chemotherapy Anal Sac Gland Carcinoma showed more favourable prognosis than surgery alone.

Keywords: Anal sac gland carcinoma, adjuvant chemotherapy, Cisplatin

Introduction
Canine anal sac gland carcinoma (ASGC) is an uncommon neoplasm originated from the apocrine gland in the walls of anal sac. ASGC represents only 2% of all canine skin neoplasms but importance of this cancer is highly invasive and metastasis character [1]. This tumour readily invades surrounding soft tissue and frequently metastasize to regional lymph node [2]. Over the past decades, numbers of new approaches have been available for treatment of metastatic ASGC, including surgical excision of both primary and secondary tumours, chemotherapy with platinum compound and radiotherapy of primary tumour mass [3-6]. Adjuvant chemotherapy is the new area in small animal medicine, only a few reports have been made on the use of chemotherapy in the treatment of ASGC. Antitumor activity of cisplatin against ASGC has been documented. Partial remission was noted in 33% of patient receiving cisplatin as a single agent [7].
The primary objective of this retrospective study was to determine whether adjuvant therapy of cisplatin would be more effective than surgery alone in Canine ASGC, using a database to provide a more complete and reliable assessment which might yield useful information for diagnosis and treatment of this tumour.

Materials and Methods
Subjects and Eligibility: This study was conducted at TVCC, West Bengal University of Animal and Fishery Sciences from January 2016 to December 2016. Subjects for this study were privately owned pet dogs with naturally occurring and histopathologically confirmed ASGC (Fig.1). Entry requirements for dog in this study included no prior cisplatin treatment, normal serum creatinine (reference range 0.5-1.5 mn/dl) and blood urea nitrogen (7- 32 mg/dl). With exception of days when dogs were undergoing clinical evaluation and chemotherapeutic treatment, the dogs lived at home with their owner.

Study Design
Cisplatin provided by Alkem Laboratories Ltd. After surgical excision 19 dogs were treated with cisplatin @ 60 mg/m^2 intravenously (admixture with 0.9% saline) once in every 3 weeks as previously described [8]. Butorphenol (Aristo Pharmaceuticals Ltd; @0.4 mg/kg i.v.) was given 20 min prior to cisplatin to decrease vomition. This therapy was delayed if serum creatinine concentration > 2.0 mg/dl or if BUN concentration >40 mg/dl. Simultaneously 11 dogs were treated with surgery alone. Two treatment groups were then compared with respect to hypercalcemia, metastatic rate and case outcome 1 year after surgical excision.

Statistical Analysis

Chi-square(X^2) test was used to determine the correlation between different biological and clinical behaviour. Survival curve(obtained by Kaplan- Meier method) were computed for further evaluating correlation between these two treatment strategies and prognosis [9]. and comparisons of survival characteristics were made between these two subgroups by means of the log-rank testing for discrete variables. Statistical analysis of collected data was performed using statistical software (GraphPad Prism 3.00; GraphPad Software, San Diego, California, USA). For all statistical analyses, *P* value of ≤0.05 was consider significant.

Results and Discussion

Hypercalcemia

A syndrome of Hypercalcemia in malignant cancer has been reported in canine [9-10]. Meuten *et al*. (1981) [11] reported that hypercalcemia was present before removal of the tumour in 20 of 22 dogs (90%) with adenocarcinoma arising from apocrine glands of anal sac and tumour removal resulted in a prompt normocalcaemia in five dogs. Meuten *et al*. (1981) [11] also reported that hypercalcemia is an useful index for detection of occult neoplasms, lying in the subcutaneous tissue adjacent to anus. Serum biochemical analysis were performed at the time of initial diagnosis. Overall 8 dogs under this study showed hypercalcemia, their calcium value ranged from 12 to 24 mg/dl. Table 1 summarized number of dogs representing hypercalcemia under treatment of cisplatin and surgery alone. Dogs treated with surgery alone showing significantly higher serum calcium (54.5%) than cisplatin adjuvant therapy (10.52%, X^2 =4.83 P<0.05).The median survival time of dogs that had surgery alone (8.73± 0.59 months) appears less than the median survival time of 10± 0.35 months in dogs under adjuvant therapy of cisplatin. Similar results have been reported by Bennett *et al*. (2002) [2], Williams *et al*. (2003) [7] also reported that survival time of 256 days for hypercalcemic dogs compared with 584 days for normo-calcaemic dogs.

Metastatic Rate

An estimation of metastatic rate (Table 2) also help to clarify activity of this chemotherapeutic agent on ASGC. The comparative analysis revealed that significant difference in metastasis rate with both of these pairing (X^2 =5.75 P<0.05). Metastasis mainly occurs via lymphatics to sacral, iliac and lumbar nodes. Therefore, we performed radiographic examination of caudal abdomen to determine lymphadenopathy of iliac lymph node. In our study, metastasis rate was 21% in dogs under cisplatin treatment after surgical excision and 72.7% in surgery alone. It was very difficult to give exact reason of high metastatic rate in patient treated with surgery alone. However, some authors reported that surgery can be helpful when metastases are confined to regional lymph node [2]. During the surgical treatment primary tumour size was generally larger than the palliative treatment. Since tumour progression is directly related to the number of proliferating cells with random mutation potentials and genetic instability [12].

Local Recurrence

The recurrence rate was listed in the Table 3. Chi square was then calculated for the overall series and found to be X^2 =5.19 with P<0.05, reviling significantly difference in recurrence rate. This present study also showed that local recurrence rate was significantly lower in dogs received cisplatin (15.78%) after surgical therapy with high mean survival time compare to surgery alone. Barnes and Demetriou reported that 42% dogs developed recurrent nodal metastatic disease after surgical extirpation of regional lymph node [3]. The contrast in between the present and earlier study may be due to the combined modality approach in chemotherapy, drugs which can effectively palliate large tumour mass may be curative when applied to minute residual tumour cell population after surgery [13].

One Year Post-Surgical Prognosis

Survival time is considered a useful criterion for evaluating prognosis of different malignancy in both man and animal [9]. In the present study, survival during of 1year after surgical debulking of tumour mass in both groups was preferred for assessment of the disease-free interval and death was consider as an event. Dogs who were still alive were censored after one year of experiment. At this time, 14/19 (73.68%) dogs under cisplatin adjuvant therapy, while 8/11 (72.73%) animals died under surgery alone (Table 4). Survival (Figure. 2) was worse in dogs having surgery alone than those received cisplatin adjuvant therapy. As mean survival time of dogs had surgery alone (8.73± 0.59) after one year was significantly lower than Cisplatin adjuvant therapy (10.74 ± 0.35, P<0.05).

Table 1: Effect of said Treatment protocols on Serum Calcium Concentration

Treatment Protocol	Serum Calcium Concentration		Total
	Hypercalcemia (%)	Normocalcemia (%)	
Cisplatin + Surgery	2(10.52)	17(89.47)	19
Surgery	6(54.5)	5(45.45)	11
Overall	8	22	30

Table 2: Effect of said Treatment protocols on Metastasis Rate

Treatment Protocol	Metastatic Rate(MR)		Total
	MR (%)	No MR (%)	
Cisplatin + Surgery	4(21.05)	15(78.94)	19
Surgery	8(72.72)	3(27.27)	11
Overall	12	18	30

Table 3: Effect of said Treatment protocols on Local Recurrence

Treatment Protocol	Local Recurrence (LR)		Total
	LR (%)	No LR (%)	
Cisplatin + surgery	3(15.78)	16(84.21)	19
Surgery	7(63.63)	4(36.36)	11
Overall	10	20	30

Table 4: One Year Post-Surgical Prognosis of said Treatment protocols

Treatment Protocol	Case Outcome		Total
	Number of Events (%)	Number of Censored (%)	
Cisplatin + surgery	3(15.78)	16(84.21)	19
Surgery	7(63.63)	4(36.36)	11
Overall	10	20	30

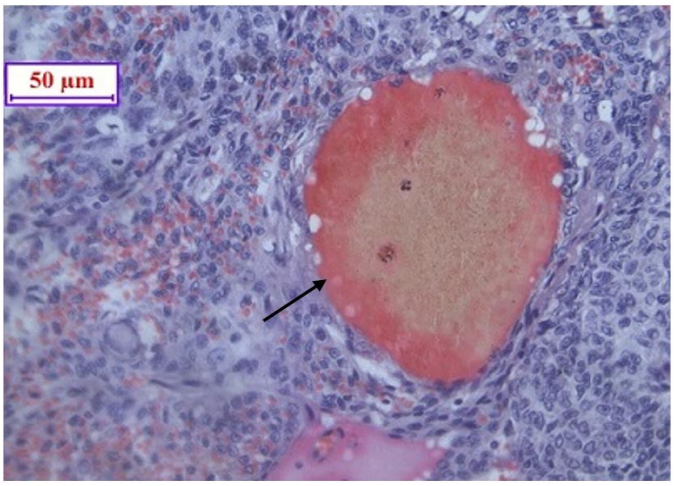

Fig 1: Anal sac gland carcinoma was characterized by well-differentiated acini formation with extensive amount of eosinophilic secretions (arrow), H and E, X 400.

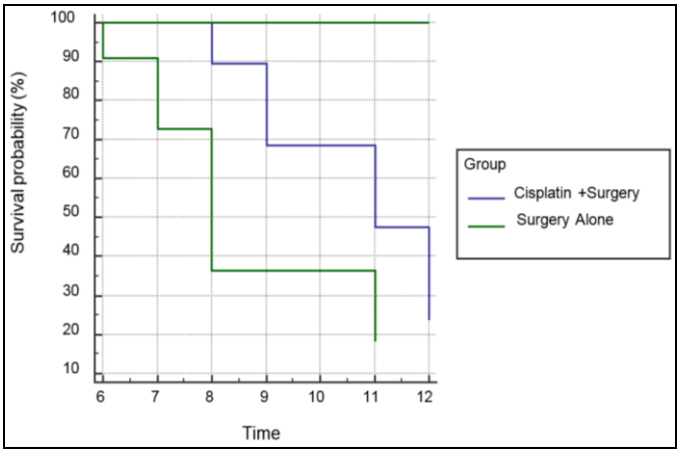

Fig 2: Survival was worse in dogs have surgery alone than those received cisplatin adjuvant therapy (*P*= 0.02).

Conclusion: Our result suggest that dogs received cisplatin adjuvant chemotherapy for Anal Sac Gland Carcinoma showed more favourable prognosis than surgery alone.

Acknowledgments: Authors are grateful to Vice-Chancellor, West Bengal University of Animal and Fishery Sciences; Dean, Faculty of Veterinary and Animal Sciences, WBUAFS and concerned Heads of the Department of Veterinary Pathology, Department of Veterinary Surgery and Radiology, WBUAFS, Kolkata, India for providing necessary facilities to do research work.

Conflict of Interest: Authors have no conflict of interest

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