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CCNU, Vinblastine and Prednisone Treatment for Grade II Dermal Mast Cell Tumor in a Yorkshire terrier dog

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Abstract : An 11-year-old, castrated male Yorkshire terrier dog was presented with multiple plaques on right inguinal region. Grade II mast cell tumor was diagnosed. The dog was treated with Vinblastine and prednisone (PDS) initially. Because of poor response of the dog, CCNU was added for more aggressive treatment. After 5 weeks treatment of with CCNU, vinblastine and PDS, the lesion was improved. Moderate leukopenia was shown after 4 cycles of chemotherapy. The chemotherapy was re-administered since the patient recovered from the leukopenia. Though the same protocol was applied, no improvement of the lesion was observed. Moreover, the general body condition of the dog became worse and was euthanized by the owner's request. Necropsy was not permitted. The survival time was 330 days after start of the chemotherapy.

Key words **:** CCNU, chemotherapy, dog, mast cell tumor

Introduction

Mast cell tumors (MCTs) are the most common cutaneous tumors in dogs, accounting for 7-21% of all skin tumors (10). The clinical behaviors and treatment responses of cutaneous MCTs in dogs can be varying from benign to highly malignant (5,8,12,16,17). There are many reports that have suggested MCTs developed in the inguinal, perineal, scrotal and preputial regions in dogs have a more aggressive biological behavior, resulting in higher recurrence rates and shorter survival times than other MCTs in other cutaneous locations (12,17,18,20). A few studies have investigated the prognosis of dogs with MCTs in the inguinal and perineal regions that have undergone adjunctive therapy before or after surgery (5,17). Systemic chemotherapy has been considered beneficial in the treatment of grade II or III MCTs when surgical excision or radiation therapy is not possible. CCNU (Lomustine) is an oral alkylating agent in the nitrosurea subclass. Clinical reports on CCNU for tumors in dogs are limited (11,14,21). CCNU as a single agent for canine MCT showed a 42% (8 of 19) response rate (14). We are reporting the case of a dog with grade II MCT in inguinal region treated with a combination of CCNU, vinblastine and PDS without surgical intervention.

Case

An 11-year-old, castrated male York-shire terrier dog was referred to the Veterinary Medical Teaching Hospital of Seoul National University with multiple plaques on right inguinal region. On physical examination, lots of disrupted pustules and multiple plaques were observed on ventral mid-abdomen and the inguinal region (Fig 1A). Enlarged lymph nodes were not palpated. Mast cell was not detected in a buffy coat smear. No abnormality was detected on radiographs of the thorax and the abdomen. Cytologically, well-differentiated MCT was diagnosed by fine needle aspiration biopsy (Fig 2). Argyrophilic nucleolar organizer regions (AgNORs) were counted to assess cellular proliferation. The mean AgNORs in 500 nuclei was 3.48 (Fig 3).

It was staged IIIb by WHO clinical staging system for MCT (multiple dermal tumors; large infiltrating tumors with or without regional lymph node involvement, without systemic signs). Excisional biopsy was performed and grade II MCTs was diagnosed by histopathology (Fig 4).

The margin of the lesion was too wide to completely excise therefore we determined to use the chemotherapeutic agents to shrink the extent of the lesion. The initial treatment was selected with vinblastine and PDS combination. Vinblastine was given as a rapid intravenous bolus at 2 mg/m^2 every 3 weeks with PDS (2 mg/kg) daily per oral and discontinued over 6 to 10 weeks with gradual tapering. After 3 cycles of initial treatments, the dog was assessed as static disease phase, therefore aggressive protocol was considered at this point. CCNU, vinblastine, PDS combination protocol was applied. PDS was administered orally at initial dosage of 2 mg/kg daily for 2 weeks, and tapered gradually. Vinblastine was given as a rapid intravenous bolus at 2 mg/m^2 on day 1, 28, 56 and 84. CCNU

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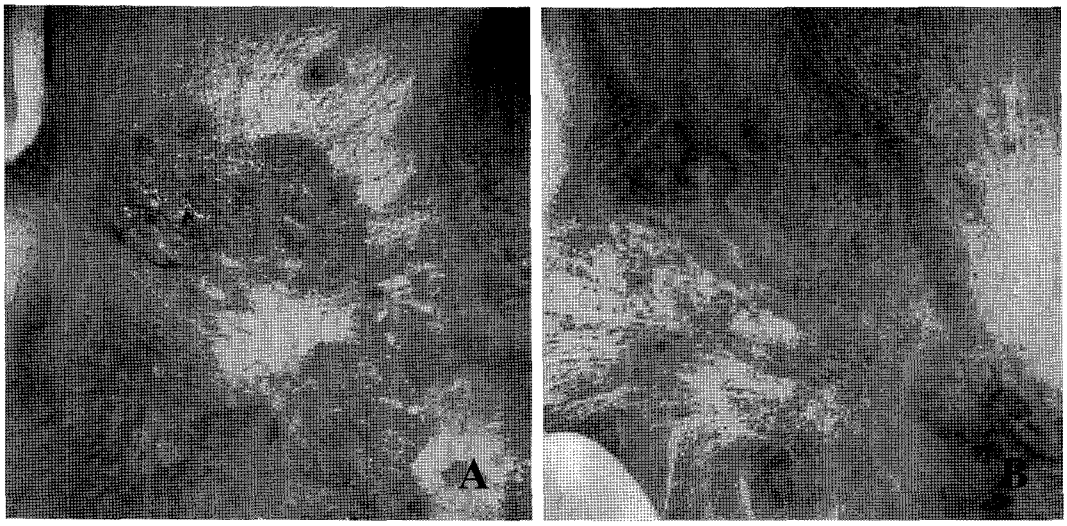

Fig 1. The inguinal lesion of a dog. A. The multiple plaques in the inguinal region before chemotherapy. B. Five weeks after chemotherapy with CCNU, vinblastine and prednisone. Note the improved lesions.

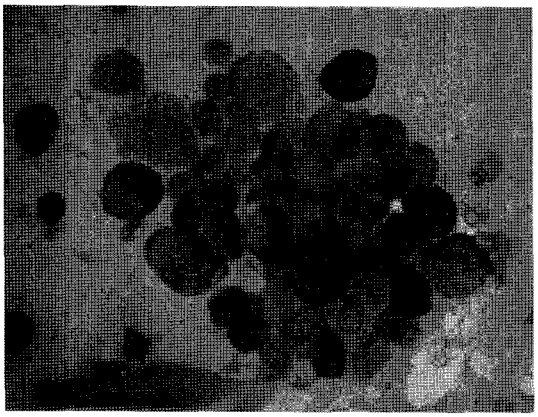

Fig 2. Cytology of the plaque in the inguinal region. Note the round cells of variable size, containing dark purple granules (Diff-Quik, X1000).

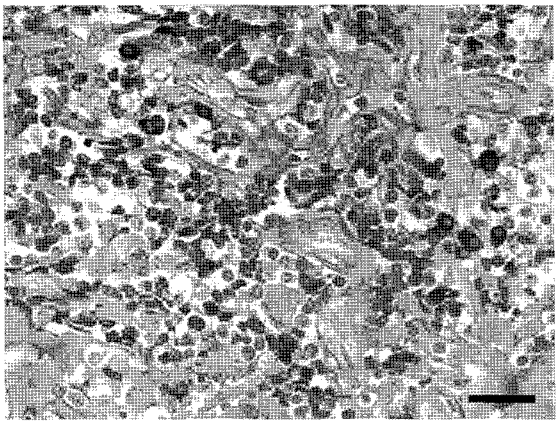

Fig 4. Histopathologic finding of the lesion. Neoplastic mast cells with poor granularity were infiltrated the dermis and extended to the dermoepidermal junction. Note moderate numbers of scattered eosinophis. H&E stain. Bar = 20 μm

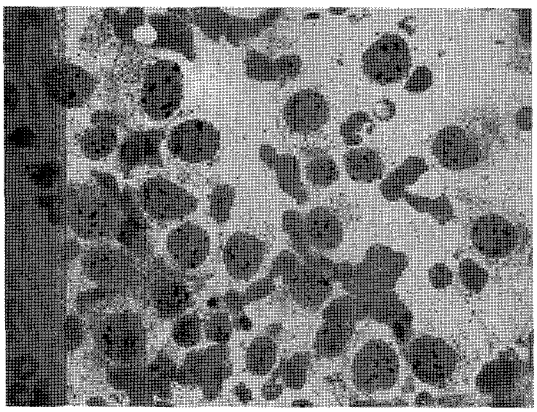

Fig 3. Argyrophilic nucleolar organizer regions counting. Several silver-stained dots are irregularly distributed and moderately variable in size, number and shape. The mean AgNORs in 500 nuclei was 3.48 (AgNOR stain, 1000)

was administered orally at a dosage of 70 mg/m^2 on day 14, 42 and the dose was increased to 80 mg/m^2 on day 70, 98. Prior to each time of chemotherapy, the total white blood cell (WBC) was counted and the liver enzyme profile was evaluated by serum chemistry every other month. Five weeks after adding CCNU in the combination, partial response was observed (Fig 1B). After four cycles of chemotherapy, moderate leukopenia (1.7×10^3/ul), fever and decreased appetite were noticed. Therefore chemotherapy was discontinued and the dog was hospitalized. After 2 weeks, general body condition of the dog was improved, however the tumor relapsed. Although the same protocol (CCNU, vinblastine, PDS) was re-administered, the dog showed severe depression and no improvement on the lesion. The dog was euthanized by the owner's request but the necropsy was not permitted. The survival time of the patient was 330 days after initiation of chemotherapy.

Discussion

The best way to treat MCTs in dogs is wide surgical excision because tumor cells often extended beyond the visual or palpable tumor margins. Incomplete excision can result in a recurrence of the tumor. Recurrence of the tumor could be more aggressive than the primary tumor because tumor cells infiltrate to deep structures and grow more rapidly (2).

Irradiation therapy decreases the risk of tumor recurrence and increases the survival time for dogs with grade II MCTs. Many reports have been described the benefit of the radiation therapy for dogs with MCTs (1,6). However, the radiation therapy was not available in this case.

Tumor grade is the most consistent prognostic indicator in dogs with MCTs (7). In two separate reports of histopathologic grading of MCTs, tumor-related mortalities were 7% and 12% for well-differentiated, 56% and 17% for intermediately differentiated, and 94% and 77% for poorly differentiated tumors respectively (3,13). In this case, a large number of intermediate and poorly differentiated MCT cells were observed (intermediate-differentiated, grade II). Clinical stage of disease also has been found to be of prognostic value for dogs with MCTs. Multiple MCTs are prone to metastasize to regional lymph node (19). In this case, the histopathologic grade was II and the clinical stage was III due to multiple inguinal lesions. Bone marrow aspiration is considered to be a more sensitive indicator of systemic involvement than the buffy coat smear, however bone marrow biopsy was not performed because evidences of metastasis was not found on physical, hematological and radiology examinations.

Chemotherapy is the most appropriate treatment option for dogs with grade II or III MCTs which are not feasible for surgery or when the radiation therapy is not available. The report using CCNU in canine MCTs showed overall response rate of 42% of complete remission, describing higher response rate than vincristine or PDS (14). PDS and vinblastine provided longer survival rate in patients with grade III MCTs with a mean survival time of 331 days (18). At the initiation of the therapy we used vinblastine and PDS, and the patient showed partial response and static disease status. Therefore we decided to use more aggressive combination protocol consisted of CCNU, vinblastine and PDS reported as effective in canine MCTs. After 5 cycles of treatments, the extent of the lesion was reduced and the total survival time was 330 days.

Treatment with this combination therapy was well tolerated in this case. The leukopenia is the most common toxicity of CCNU and vinblastine. Although the moderate leukopenia observed after treatment with CCNU, the clinical signs were not severe and recovered within 3 days. CCNU-induced hepatotoxicity was developed in 6.1% (11 of 179) of different tumor-bearing dogs (9). In this case, no clinical signs related to hepatotoxicity including weight loss, polyuria/polydipsia and abdominal distention were observed and liver enzyme levels in serum were remained in reference range.

Although a recent study suggested that dogs with MCTs in inguinal and perineal regions did not have poorer prognosis than the MCTs in other cutaneous locations (17), this dog showed aggressive and rapid biological behavior.

AgNORs indirectly determines the rate of cell proliferation. A higher AgNOR count has also been associated with a shorter survival time (4,16). In recent study suggest median AgNOR in 100 nuclei was 1.2 for nonrecurring MCTs and 1.5 for recurring MCTs (16). Another study suggest that hazard score significantly relating short survival time for canine MCTs was 2.57 (15). In this case, the AgNOR count was higher than previous reports (16) as 3.84 predicting clinical behavior could be aggressive at the time of diagnosis.

Conclusion

In conclusion, the combination of CCNU, vinblastine and PDS had some benefits in treatment for advanced MCTs that showed reluctance to other drugs when the surgery or radiation therapy is not available. The toxicities related to this combination including leukopenia and hepatotoxicity were minimal. Although this dog had many negative prognostic factors including high AgNOR ratio, relapsing of the tumors, the location of the tumor (inguinal) and clinical staging (multiple, large infiltrating tumors), the survival time was longer than we expected as a 330 days after initiation of chemotherapy.

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CCNU, Vinblastine과 Prednisone으로 병용 치료한 요크셔 테리어 개의 Grade II 피부 비만세포종 증례

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요 약 : 11살의 중성화 수컷 요크셔 테리어 개가 오른쪽 서혜 부위에 다발성의 plaque를 주증으로 내원하였다. 조직학적 검사를 통해 grade II 의 비만 세포종으로 진단되었다. 초기 치료는 Vinblastine과 Prednisone을 사용하였다. 그러나 치료 반응이 좋지 않아 Lomustine (CCNU)를 첨가한 공격적인 치료를 실시하였다. CCNU, Vinblastine, PDS를 이용한 치료 5주 후에 병변은 개선되었다. 4차 항암치료 시 중등도의 백혈구 감소 증을 나타내었고, 이에 대한 개선 처치 후에, 같은 프로토콜을 적용한 항암치료를 실시하였으나, 병변이 개선되지 않았다. 이후, 환자의 전신적인 상태가 나빠져 보호자의 요청에 의해 안락사 하였으나 부검은 실시하지 못하였다. 환자의 생존기간은 항암치료 개시 후 330일 이었다.

주요어 : 개, 비만세포종, 항암제치료, CCNU