Note

Palliative effects of non-selective intra-arterial chemotherapy of paclitaxel plus platinum combination in two dogs with intranasal cancers

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Abstract

Non-selective intra-arterial (I-A) chemotherapy of paclitaxel plus platinum combination was performed in two dogs with cancers of the nasal cavity, including undifferentiated (Case 1) and transitional (Case 2) carcinomas. The drug dosages were reduced to 25% to 35.5% of the typical doses for systemic chemotherapy, and they were perfused via common carotid arteries. Case 1 had marked regression of the cancer but survived for only 53 days after the therapy. Case 2 had partial remission for approximately 3 months and survived for 126 days. Adverse events of the chemotherapies were not induced in Case 1, but mild adverse events were seen in Case 2. Non-selective I-A chemotherapy in this report required easy and simple procedures and could be safely performed via a reduction of the dosages of the drugs. Although future research will address issues concerning the intervals, frequencies, and drug dosages, the I-A chemotherapy was suggested as being able to contribute to palliative remission in canine intranasal cancers.

Key words : dog, intra-arterial chemotherapy, nasal cancer, paclitaxel, platinum

Canine nasosinal neoplasms represent approximately 1% of all tumors in dogs [17]. The major malignancies include adenocarcinoma, transitional carcinoma, squamous cell carcinoma, undifferentiated carcinoma, chondrosarcoma, fibrosarcoma, osteosarcoma, and lymphoma [17].

Single or multimodal treatments, including surgery, chemotherapy, and radiation therapy, are performed in dogs with cancers of the nasal cavity [17]. Proton beam radiotherapy, brachytherapy, cryotherapy, and photodynamic therapy have been also investigated for treating the disease [17]. Median survival time is 95 days in dogs that receive no treatment and approximately 3 to 6 months post-surgery in dogs that receive treatment [17]. Chemotherapies using platinum, doxorubicin, and oral piroxicam were applied in canine patients with intranasal cancers. The median survival time ranged from 5 to 7 months [8, 12]. As a single modality of treatment, radiation therapy with cobalt or linear accelerator has shown the most favorable outcomes in dogs with nasal cancers, with median survival time beyond 6 months in most reports [4, 13, 16, 17].

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Although radiation therapy remains a problem for the local recurrence of the cancers, it has the potential for improved survival of a dog with a recurrent tumor [5].

Intra-arterial (I-A) chemotherapy can induce high concentrations of anti-neoplastic agents in cancer tissue by injection into the artery feeding to the tissue [1]. In human patients with head and neck cancers, this chemotherapy has been combined with radiation therapy, and the combination has shown good outcomes of organ preservation and survival [2, 6, 7, 19]. In veterinary medicine, however, there has been little information concerning I-A chemotherapy for head and neck cancers in dogs and cats. Kobayashi et al. [11] reported the I-A chemotherapy via a reservoir system for orbital osteosarcoma in a dog and discussed its efficacy.

Platinum, *cis*-diamminedichloroplatinum (CDDP), and *cis*-diammine (1,1-cyclobutanedi-carboxylato)-platinum (CBDCA), has been used to treat human and canine patients with head and neck cancers [2, 6, 7, 11, 19]. The concomitant use of taxane has produced better outcomes in the human patients [6, 7]. Paclitaxel (PTX), one of the taxoids, is not commonly used in small animal medicine although there have been a few reports of the utility in treating malignant tumors in dogs and cats [9, 10, 15]. The compound exerts an anti-tumor effect by stabilization of microtubule and inhibition of its depolymerization, resulting in mitotic arrest [3, 10]. The authors speculated that the combination of I-A chemotherapy with taxane and platinum might provide favorable outcomes in canine intranasal carcinomas originating in epithelial cells similar to the outcomes in human patients with tongue and laryngeal squamous cell carcinoma [6, 7]. To the authors' knowledge, however, there has been no report concerning canine nasal cancers treated with the I-A chemotherapy of the combination alone.

In this paper, the authors describe the procedure and performances of the I-A chemotherapy of PTX combined with platinum in two dogs with intranasal cancers. We also discuss the future of I-A chemotherapy for the treatment of canine nasal carcinomas.

Case 1

An 8-year-old male Beagle weighing 16 kg was presented with swelling of the left forehead, which had persisted for 2 months. At the first admission, physical examination revealed slight protrusion of the left eye, hyperemia of the conjunctiva, and a viscous brownish nasal discharge. Hematology revealed no significant findings except leukocytosis (26,700/ μ l). Radiographical examination indicated osteolysis of the nasal bone to frontal sinus and radiopacity of the left nasal cavity. Computed tomography (CT) examination demonstrated a neoplastic lesion extensively occupying the nasal cavity to the frontal sinus and invasion of the tumor into the left orbita, resulting in compression of the left eyeball (Fig. 1). Histopathological

Fig. 1. CT findings of Case 1, showing the presence of large amounts of cancer tissue in the nasal and frontal sinus cavities with severe osteolysis and compression of the eyeball caused by invasion of the cancer (1A, 1B, 1C).

examination of the tissue biopsy samples showed undifferentiated carcinoma. The clinical stage in this dog, according to the staging system of the World Health Organization (WHO), was T3N1M1. I-A chemotherapy with PTX and the CDDP combination were scheduled in the dog. Under general anesthesia with induction by propofol and maintenance with isoflurane,

a skin incision was made in the left cervix to approach the left common carotid artery. An 18-gauge indwelling needle was inserted into the carotid artery of the dog, and PTX 30 mg (TAXOL, Bristol-Myers KK., Japan) and CDDP 15 mg (Cisplatin Nichi-Iko Pharmaceutical Co., Ltd, Japan) were infused in that order. These dosages were reduced by approximately 35.5 % (PTX) and 33.4 % (CDDP) of the recommended dosages (PTX 132 mg/m², CDDP 70 mg/m²), respectively [3]. Prior to PTX infusion, premedication, including diphenhydramine (4 mg/kg, VENASMIN, Towa Pharmaceutical Co., Ltd, Japan), cimetidine (4 mg/kg, Tagamet, Sumitomo Dainippon Pharma, Co., Ltd, Japan), and prednisolone (2 mg/kg, PREDONINE, Shionogi & Co., Ltd, Japan), was administered to prevent anaphylactic shock caused by PTX. In addition, the drug preparations were diluted ten fold for PTX and two fold for CDDP with 0.9% NaCl solution before infusion. The speed of the drug infusion was set by regulating the speed of the intravenous administration [3]. In brief, PTX was infused with 30 ml/hr for the initial 30-min period, and then the speed was increased to 60 ml/hr after confirming there was no allergic reaction. Following the PTX infusion, CDDP was administered over 20 min. The dog also received a sufficient amount of 0.9% NaCl solution pre- and post-I-A chemotherapy. Bleeding after the needle removal was controlled by pressure hemostasis. Serious adverse effects did not develop in the dog during the infusion or post-chemotherapy.

On day 18 after the chemotherapy, the dog showed improved clinical conditions with visual changes in the facial architecture, and CT examination was performed to evaluate the lesions. The results demonstrated marked regression of the lesion in the nasal and frontal sinus cavities and successful recovery of the eye (Fig. 2). However, a small amount of the neoplastic lesion remained in the right nasal cavity opposite the treated site.

Fig. 2. CT findings of Case 1, showing striking regression of the cancer tissue on day 18 after I-A chemotherapy (2A, 2B, 2C).

On day 30 after the chemotherapy, the dog showed lameness in the left forelimb. Radiology revealed osteolysis of the olecranon, indicating metastasis of the cancer. On day 39 after the chemotherapy, CT examination confirmed no obvious progression of the cancer (Fig. 3), although the remained lesion of the right nasal cavity minimally progressed. Regeneration of the nasal bone, which had been affected by the cancer, was also observed (Fig. 3). Because distant metastasis and recurrence

Fig. 3. CT findings of Case 1, showing no marked progression of the disease (3A, 3B, 3C), despite minimal recurrence in the right nasal cavity on day 39 after chemotherapy. Regeneration of the nasal bone, which had been affected by the cancer, is apparent in 3A and 3B.

of the cancer were suspected, intravenous systemic chemotherapy of PTX 30 mg plus CDDP 45 mg was administered on day 47 after the first chemotherapy. On days 48 and 53 after the first chemotherapy, 5-Fluorouracil (5-FU, Kyowa Hakko Kogyo Co., Ltd, Tokyo) at 150 mg/m² was also administered, following the regimen of the therapy used for head and neck cancers

in human patients [6, 7]. During the chemotherapies, although the dog showed no improvement, there was no progression of the cancer. On day 54 after the first chemotherapy, the dog was found dead a few hours after breakfast. Autopsy was permitted by the owner. Pathology demonstrated the presence of the cancer with hemorrhage in the nasal and frontal sinus cavities and metastasis of the cancer in the submandibular, superficial cervical, and axillary lymph nodes and olecranon.

Case 2

An 11-year-old spayed female Shiba dog weighing 12.6 kg presented with a history of nasal bleeding from the right nostril, which had persisted for approximately 1 month. In the first presentation to our hospital, there were no visual deformities of the face. Hematology revealed no abnormal findings except leukocytosis (28,600/ μ l). Radiographical examination suggested low radiolucency in the right nasal cavity. CT examination demonstrated a neoplastic lesion in the right nasal cavity (Fig. 4). Histopathological diagnosis of tissue samples was transitional carcinoma. The clinical stage in this case was T1N1M1,

Fig. 4. CT findings of Case 2, showing the unilateral presence of the cancer tissue in the right nasal cavity (4A, 4B, 4C).

on the basis of the WHO staging system. On day 25 after the first presentation, I-A chemotherapy of PTX 18 mg (33 mg/m², TAXOL) and CBDCA 40 mg (75 mg/m², PARAPLATIN, Bristol-Myers KK., Tokyo) was administered via the right common carotid artery using a 22-gauge indwelling needle, as in Case 1. The dosages of both drugs were also reduced to 25% of the recommended amounts, similar to Case 1. Premedication was also prescribed prior to PTX infusion. The speed of PTX infusion was the same as in Case 1. CBDCA was diluted two fold with 5% glucose solution, and a bolus was administered into the artery. Post-chemotherapy, mild nasal bleeding and sneezing were occasionally observed during hospitalization. Adverse responses, including vomiting (Grade 1), diarrhea (Grade 1), and some anorexia (Grade 2) related to the chemotherapy, were mild in this case. On day 7 post-chemotherapy, hematology confirmed thrombocytopenia (126,000/ μ l), possibly related to the bleeding, and the dog received a blood transfusion of 100 ml.

On days 16 and 44 post-chemotherapy, CT examinations demonstrated partial remission of the cancer in the right nasal cavity (Fig. 5, Fig. 6). The owner did not request second chemotherapy because of the clinical improvement in nasal bleeding

Fig. 5. CT findings of Case 2, showing partial regression of the cancer tissue on day 16 after I-A chemotherapy (5A, 5B, 5C).

Fig. 6. CT findings of Case 2, showing more regression of the cancer tissue on day 44 after I-A chemotherapy (6A, 6B, 6C) compared to day 16 in Fig. 5.

and financial concerns. Piroxicam (0.3 mg/kg) was prescribed, and the dog did not develop nasal bleeding for 3 months.

However, the dog presented with recurrence of nasal bleeding and swelling of the nose on day 92 post-chemotherapy. The owner agreed to the second I-A chemotherapy in the dog. Prior to the chemotherapy, CT examination was performed, which revealed recurrence of the cancer involving the nasal bone and sieve plate, indicating progression of the disease. On day 100 after the first chemotherapy, the dog received the second chemotherapy in the same procedure and dosages as in the first chemotherapy. The dog showed epistaxis during hospitalization for 3 days after the second chemotherapy, but no bleeding was seen after discharge. Alimentary signs, including diarrhea (Grade 1) and vomiting (Grade 1), possibly caused by PTX, developed 2 days after the second chemotherapy. Furthermore, the dog had severe nasal bleeding on day 19 after the second chemotherapy. The dog also showed neurological signs, including blinking, wandering in the room, and convulsions. The owner phoned to inform about the death of the dog on day 126 after the first chemotherapy. Postmortem examination was not performed in this case.

The authors had expected that the combination I-A chemotherapy of taxane plus platinum would have provided favorable anti-neoplastic efficacies in our patients, similar to the outcomes in human patients with head and neck cancers [6, 7]. The results showed marked or partial remissions and tentative clinical improvements with mild adverse reactions in the dogs.

Chemotherapeutics for cancer therapies damage both normal and tumorous tissues, and they occasionally cause undesirable events, such as myelosuppression and gastrointestinal and renal toxicities [3]. PTX has a high potential for an anti-neoplastic effect, but severe adverse events usually develop after its administration [3, 9, 15]. The main events are severe leukopenia and gastrointestinal toxicity, including diarrhea and vomiting [3, 9, 15]. In this paper, only Case 2 developed those gastrointestinal events after the chemotherapy, which was suspected to be induced by PTX. Our experiences of PTX administration in dogs have shown that there are individual differences in sensitivities to PTX, regardless of the injection routes and doses of PTX. Platinum, especially CDDP, is also well known to lead to renal toxicity [3]. However, no such events concerning the I-A perfusion of platinum were demonstrated in our dogs. The selection of platinum, either CDDP or CBDCA, would depend on the patient's condition or underlying diseases, such as chronic heart and renal failures. In Case 2, CDDP was substituted to CBDCA because of unnecessary hydration and lower toxicity. 5-FU was also administered intravenously twice in only Case 1, but the effect was uncertain.

Determination of the drug dosage has been also one of the subjects in the I-A chemotherapy. In human patients with head and neck cancers, 50-60 mg/m² docetaxel and 50-60 mg/m² CDDP have been infused into arteries [6, 7], and these doses are about the same as doses used with intravenous administration, as described in the drug package inserts. On the contrary, there have been no reports on the I-A chemotherapy of taxanes in dogs with the cancers. Doses of CDDP for I-A infusion have not been evaluated in dogs with the cancers, and only one article, by Kobayashi et al. [11], has proven to be a useful reference. In this report, the dogs received PTX and platinum at dosages less than their recommended amounts for each drug [3]. The authors confirmed that the combination provided an anti-neoplastic effect in a cultured cell line of canine malignant tumor, even though their concentrations were low (unpublished). In addition, the authors reported that intravenous chemotherapies in the combination with reduced doses of each drug could have controlled pleural effusion caused by pulmonary metastasis of

ovarian adenocarcinoma in a dog [9]. In our dogs reported in this communication, the drugs were injected into the common carotid arteries close to the nasal lesions according to antegrade blood flow. The target would have been exposed to high concentrations of drugs by injecting them into the arteries close to the lesion, even though smaller doses of the drugs were used. Furthermore, the reductions in dosages were expected to contribute to the prevention of adverse effects and the shortening of anesthesia time, leading to lower cost of the treatment.

In this report, I-A chemotherapy was achieved by inserting an indwelling needle into the common carotid arteries and by the non-selective perfusion of drugs to the cancer tissues in the dogs. This procedure did not require the insertion of an angiographic catheter or guide-wire with fluoroscopic guidance after arterial angiography. In cases that owners request minimally invasive treatments, however, percutaneous I-A infusion through angiographic catheters with fluoroscopic guidance via femoral or carotid arteries [18] or reservoirs [11] should be considered, although their financial constraints will increase.

In human patients with head and neck cancers, super selective I-A chemotherapy combined with radiation therapy has led to excellent outcomes [6, 7]. The authors also had experiences in selective I-A chemotherapies using an angiographic catheter guided by fluoroscopy via the maxillary artery in dogs with intranasal cancers. However, acute renal failure developed in the dogs within 1 week after the chemotherapy even though the drug dosages were reduced (unpublished). The authors surmised that the renal failure could have been associated with tumor lysis syndrome induced by the excessive concentration of the drugs delivered by the selective I-A chemotherapy in the cancer tissues. In human patients, tumor lysis syndrome after chemotherapy occurred in lymphoproliferative malignancies [14], but the condition caused by the selective I-A chemotherapy have been also reported in solid tumor cases [14]. Nakamura et al. [14] described that the syndrome occurred mainly in tumors with high and moderate sensitivity to therapy and noted that other systemic therapies for solid tumors might increase the responses to chemotherapy. In addition to these factors, in dogs with intranasal cancers, the lesions are usually detected after clinical signs develop and the neoplasm has already grown excessively to occupy the unilateral or bilateral nasal cavities. The volume of the lesion may be also related to the tumor lysis syndrome after selective I-A chemotherapy.

In both Case 1 and Case 2, the dogs could not receive radiation therapy because of the time and financial constraints of the owners. In addition, surgery was rejected because it would have resulted in the incomplete resection of the cancers and cosmetic changes to the dogs' faces. Although systemic chemotherapies for canine intranasal cancers were reported by Hahn et al. [8] and Langova et al. [12], the chemotherapy would have been expected to need rounds of the treatments. Accordingly, the authors designed a non-selective I-A chemotherapy performed using easy and simple procedures and with only a few rounds of the treatment required for our dogs. Prior to chemotherapy, we had misgivings about other negative effects, including damage to the eyes and brains. In this report, neither dog developed these events. Neurological signs were observed in Case 2, but the condition was estimated to be due to progression of the cancer because of sieve plate destroyed. In this report, the survival times were almost as short as if the dogs had received no treatment or only surgery [17]. However, the numbers of dogs and cancers were limited in only two, and the protocols of the chemotherapy were pilot regimens. In future research, the protocols, including the intervals, frequencies, dosages of the drugs, and the infusion speeds for the I-A chemotherapy will be constructed for dogs with intranasal cancers.

In conclusion, non-selective I-A chemotherapies were easily and safely achieved in 2 dogs described here, and they were evaluated for temporal partial remissions of the cancers after the chemotherapies. In addition, the adverse events were mild in these dogs, presumably associated with reduction of the drug dosages. To the author's knowledge, this is the first report concerning I-A chemotherapy of PTX plus platinum combination for canine intranasal cancers.

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パクリタキセル / 白金製剤併用非選択的動注化学療法により緩和効果が得られた鼻腔内悪性腫瘍の犬 2 例

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■ 和文要約

鼻腔内の未分化癌(症例1)、移行癌(症例2)と診断された犬2例に対し、パクリタキセル/白金製剤併用の非選択的動注化学療法を行った。それぞれの投与量は全身化学療法の推奨量の25%から35.5%に減量し、総頸動脈から注入した。症例1は著しい腫瘍の減容積が得られたが、治療後の生存期間は53日であった。症例2においても約3カ月間部分寛解が得られたが、治療後の生存期間は126日であった。本療法による副作用は、症例1ではみられず、症例2においても軽度であった。本報告における非選択的動注化学療法は、手技が容易かつ簡便であり、投薬量の減量により安全に実施し得た。本療法は、その間隔、回数および薬剤の投与量に課題が残るものの、犬の鼻腔内悪性腫瘍に対し、緩和効果が得られる可能性が示唆された。

Key words : dog, intra-arterial chemotherapy, nasal cancer, paclitaxel, platinum

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