

Adjuvant Metronomic Chemotherapy in a Dog with Nasal Transitional Carcinoma

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Abstract : A four-year-old spayed female Maltese dog weighing 3 kg was referred with reverse sneezing and four-month history of unilateral nasal discharge. She was diagnosed as nasal transitional carcinoma which in bilateral nasal cavity and extending into the frontal sinus by biopsy with rhinoscopy. Metronomic chemotherapy with cyclophosphamide (12.5 mg/m²) and toceranib phosphate (2.5 mg/kg) was initiated following after surgical treatment of nasal mass debulking. Clinical response was good and had no side effects during the chemotherapy period (11 months after diagnosis). This is a case report describing adjuvant metronomic chemotherapy in nasal transitional carcinoma in Korea.

Key words : cyclophosphamide, metronomic chemotherapy, nasal transitional carcinoma, surgical debulking, toceranib.

Introduction

Tumors of the nasal cavity and paranasal sinuses account for approximately 1% of all neoplasms in dogs (7). Nasal tumors, the majority of which are malignant in both dogs and cats, most commonly found in the nasal cavity (7). Nasal tumors are primarily only locally invade the frontal and other para nasal sinuses, although metastasis occurs infrequently (11). There are several types of nasal carcinoma that have been estimated to occur at the following frequencies: adenocarcinoma, 33%; transitional carcinoma, 26%; squamous cell carcinoma (SCC) 26%; and undifferentiated carcinoma, 15% (11).

The most common clinical sign of a nasal tumor is unilateral or bilateral nasal discharge, which is usually mucopurulent and may be bloodstained. Advanced cases tend to cause facial deformity and epiphora (8).

The only treatment regimen that has been proven to be of benefit is radiotherapy, either in the presence or absence of surgical debulking (4,8). A comparison of survival times in dogs with nasal adenocarcinoma found that neither chemotherapy nor surgical removal influenced survival time. However, dogs given radiotherapy had significantly improved survival times (4).

Recently adjuvant metronomic chemotherapy with toceranib phosphate has been considered useful to in the management of nasal cavity neoplasm (5).

Here, we report a patient who presented with chronic nasal discharge due to the presence of a nasal transitional carcinoma, the patient's prognosis was guarded but has been well managed with adjuvant metronomic chemotherapy with cyclophosphamide and toceranib phosphate after surgical removal.

The patient has survived 11 months after diagnosis without recurrence of clinical signs or adverse effects of metronomic chemotherapy.

Case

A four-year-old spayed female Maltese dog weighing 3 kg was referred to Chungnam National University Veterinary Medicine Teaching Hospital presenting with unilateral nasal discharge and reverse sneezing that had been present for four months. On physical examination, the patient was clinically normal with the exception of open mouth breathing. A complete blood count (CBC) and serum biochemical parameters were within reference ranges. Skull radiography revealed increased opacities on the right side of nasal cavity and irregular margins of nasal turbinate (Fig 1). Rhinoscopy was performed and mass was found in the right nasal cavity. On histopathological examination, the nasal mass was diagnosed as a nasal transitional carcinoma. Microscopically, the nasal mass consisted of a palisading arrangement of columnar cells that was perpendicular to the basement membrane (Fig 2B). The neoplastic pleomorphic cells had indistinct cell borders and an increased nuclear-to-cytoplasm ratio. The cytoplasm in neoplastic cells was basophilic and contained numerous vacuoles. A well-defined basement membrane was present beneath the stratified layers of neoplastic cells. These neoplastic cells showed strong invasion to adjacent bony tissues (Fig 2C).

Computed Tomography (CT) scanning was performed to compare the invasiveness of the nasal mass with nearby tissues and to accurately locate the mass (Fig 3). Soft tissue was found throughout the entire right nasal cavity, part of the left nasal cavity, and also in the frontal sinuses which was suspected to be a nasal mass. CT scanning revealed bone lyses in the cranial nasal turbinate, all of the right ethmoidal

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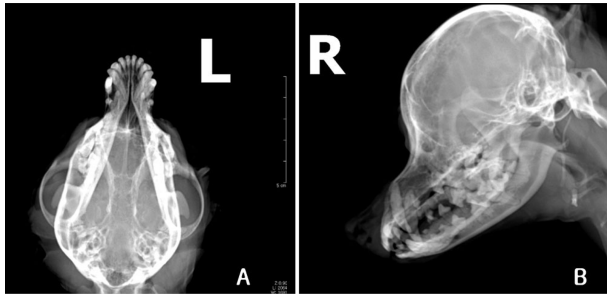


Fig 1. Radiography of the skull. Dorsoventral (A) and lateral (B) view. Radiographs revealed increased opacities on the right side of nasal cavity and irregular margins of nasal turbinate.

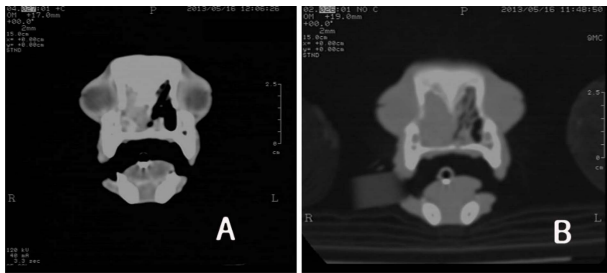


Fig 3. Soft tissue transverse contrast CT enhancing image (A) and bone transverse CT image (B). Soft tissues were found in the entire right nasal cavity, part of the left cavity, and also in the frontal sinuses which were suspected to be a nasal mass (A). Bone lyses were found not only in the cranial nasal turbinate, but also in all of the right ethmoidal bones and caudally bilateral.

bones and the caudally bilateral palatine and frontal bones. Dorsal rhinotomy was performed in order to surgically debulk the nasal mass. Several masses of 2-3 mm in size were carefully removed (Fig 2A). Immediately after removal of the mass during surgery, umbilical tape dampened with carboplatin (Carplan Infu[®], Donga, Korea, 100 µg/ml) was packing inside the cavity. Adjuvant metronomic chemotherapy with cyclophosphamide (Alkilozan tab[®], Ildong, Korea) and toceranib phosphate (Palladia[™], Pfizer, Italy) was initiated twelve days after surgery, low dose of cyclophosphamide (12.5 mg/m² per os (PO), once a day) and toceranib phosphate were prescribed (2.5 mg/kg PO, once a day) with gastrointestinal protectants. A two-week term of recheck, urinalysis, and skull radiography were performed and clinical response was

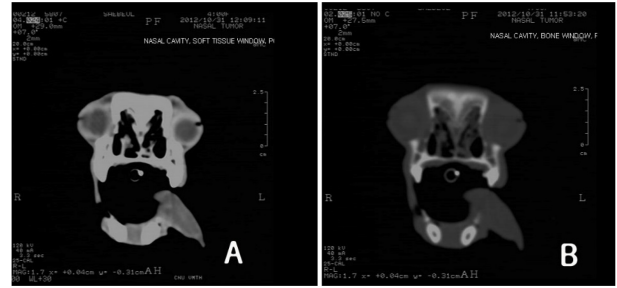


Fig 4. Soft tissue transverse contrast CT enhancing image (A) and bone transverse CT image (B). Scattered Fluid/soft tissue density that are considered to be residual from the surgery were found in the nasal cavity. (A). Maxillary and palatine bone osteoanagenesis was found (B).

good. There were no signs of side effects including bone marrow suppression, hemorrhagic cystitis, or gastrointestinal problems (i.e. anorexia, vomiting, and diarrhea). Patient has remained clinically symptom-free for eleven months and a CT scan recheck was performed for a more objective prognosis assessment at seven months. Upon the CT scan recheck, there was no evidence of recurrence and metastasis (Fig 4). With CT scan recheck, we maintained metronomic chemotherapy.

Discussion

In veterinary medicine, nasal carcinoma in dogs is characterized by aggressive local invasion, as demonstrated by the ability of the tumor to extend through the cribriform plate into the brain (8). The prognosis for nasal tumors is guarded. Without treatment, the prognosis for dogs with nasal carcinomas is approximately three to six months due to local invasion (8). A comparison of survival times in dogs with nasal carcinoma found that dogs given combination therapy with surgery after radiation had significantly increased survival times, the median survival time (MST) after combination therapy with surgery and radiation was 47 months (1). The MSTs of alternative therapies were radiotherapy alone, 19 months (1) and chemotherapy alone, five months (3).

Combination therapy with radiation and surgery is the best therapeutic option. However, it cannot be applied to all patients due to economic issues or the lack of an available radiation therapy facility.

Metronomic chemotherapy is the continuous administra-

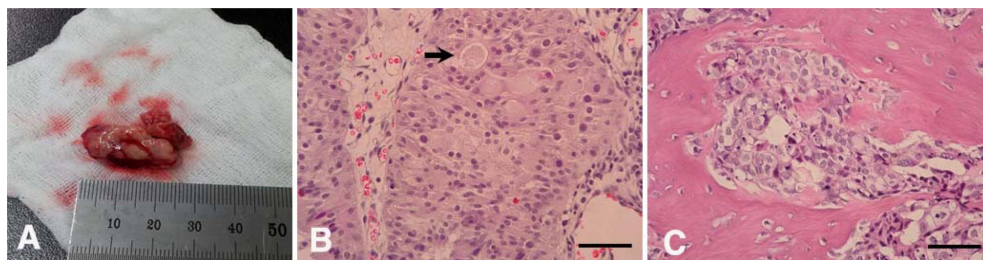


Fig 2. Dorsal rhinotomy was performed in order to surgically debulk the nasal mass. Several masses of 2-3 mm in size were carefully scraped (A). The irregular nasal carcinoma mass consisted of palisading arrangement of columnar cells that was perpendicular to the basement membrane. Note microcyst (arrow) within the tumor cell layer (B). Note infiltrative growth of tumor cells in the bone tissue (C). H&E, Bar = 50 µm.

tion of low dose chemotherapy drugs so susceptible cancer cells are continuously to chemotherapeutic drugs without a rest period, this method results in the inhibition of tumor blood vessel growth (6). There are three specific aspects of angiogenesis have been shown to be impacted by continuous chemotherapeutic schedules. The first is a cytotoxic effect on the endothelial cells of the blood vessels themselves, the proliferation and migration of endothelial cells are directly inhibited. The second means of decreasing angiogenesis appears to be an indirect effect mediated by elevation of the endogenous angiogenesis inhibitor thrombospondin-1 (TSP-1). TSP-1 modulates growth factors, thereby preventing further vessel expansion. Finally, suppression of bone marrow-derived circulating endothelial progenitor cells (CEPs) may inhibit angiogenesis as, the expansion of tumor blood vessels may also require, or at least be influenced by, recruitment of CEPs (9). Metronomic chemotherapy also suppress regulatory T cell (T-reg) and this is another effect of anti-tumor immunity (6,9).

The anti-angiogenic effect of continuous chemotherapy protocols results from the ability of tyrosine kinase inhibitor (TKI) drugs such as toceranib phosphate to react against various blood vessel growth factors (6). Orally bioavailable toceranib phosphate was developed as an anti-angiogenic agents based on its inhibition of vascular endothelial growth factor receptor (VEFG-R) and platelet-derived growth factor receptor (PDGF-R), two receptor families known to play an important role in tumor driven angiogenesis (5). The dose for toceranib phosphate is 2.5-3 mg/kg every-other-day or Monday, Wednesday, and Friday (6). Side effects include GI toxicity, anorexia, vomiting, diarrhea and mild, non-life threatening neutropenia (6).

Cyclophosphamide is another metronomic chemotherapy drugs, cyclophosphamide is an alkylating agent that has been shown to suppress T-regs, and inhibit angiogenesis by increasing TSP-1 levels and suppressing CEP recruitment (2). The dose of cyclophosphamide is 10-25 mg/m² daily to every-other-day. Side effects include bone marrow suppression and sterile hemorrhagic cystitis (2).

Umbilical tape dampened with very low dose of carboplatin (100 µg/ml) was used to pack the area of surgical debulking. The dilution dose was selected according to preliminary data (10). It was not a chemotherapeutic dosage (300 mg/m² in dogs), however, it may prevent seeding of neoplasms during surgical debulking. The patient showed no adverse effect or irritation.

We know that radiotherapy is the most effective therapy for nasal tumors yet given its high cost and the lack of radiation therapy facilities, this therapy may not be readily accessible for many world clients. Therefore, in this case, combination therapy with metronomic chemotherapy after surgical debulking can be an alternative option to improve patient's quality of life (QOL) and extend survival time. In this patient, the nasal mass had already invaded the frontal sinuses, bone lyses from the cranial nasal turbinate, all of the right ethmoidal bones and the caudally bilateral palatine and frontal bones were found by CT scan. Surgical debulking was conducted to relieve tumor burden and improve respiratory distress. Therefore, a complete and clean tumor free

margin was not expected. Umbilical tape pack with carboplatin prevented the tumor seeding, effect that can occur after surgical removal of the main tumor. Metronomic chemotherapy with cyclophosphamide and toceranib phosphate delayed tumor regrowth, and tumor invasion in the local area. Specially, toceranib phosphate was dosed every day as opposed to every other day which has been previously reported (6). There were no reported side effects of treatment.

This patient has survived for 11 months since the diagnosis has been made, without recurring clinical signs.

Conclusion

In patients with nasal carcinoma, metronomic chemotherapy with surgical debulking and umbilical tape packing with carboplatin can be a good alternative treatment option for maintaining patient's QOL and extending survival time.

Acknowledgement

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cavities in 77 dogs. J Am Vet Med Assoc 1993; 202: 1469-1475.

개의 비강 이행암종에서 메트로노믹항암 요법

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요 약 : 4살령의 중성화 암컷 말티즈 견이 4개월에 걸친 편측성 코 분비물 및 코막힘을 주증으로 본원에 내원하였다. 환자는 비강 이행암종이 전두동까지 파급되어 있는 것이 비강 내시경을 통해 확인되었다. 보조적 항암치료로 사이클로포스파마이드(12.5 mg/m^2) 와 티로신 키나아제 억제제인 토세라닙(2.5 mg/kg)을 수술적 부피 감량술 이후에 적용 하였다. 치료반응은 양호 하였으며, 진단 후 11개월 동안 항암치료에 대한 부작용 없이 잘 유지 되었다. 본 증례는 국내에서 비강 이행암종에서 보조적 항암치료를 실시한 최초 보고이다.

주요어 : 사이클로포스파마이드, 메트로노믹 항암요법, 비강 이행암종, 수술적 부피감량술, 토세라닙