https://doi.org/10.17221/85/2021-VETMED

Adjuvant therapy with imatinib for an incompletely resected multilobular tumour of bone in a dog

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Citation: Lee SH, Kim DH, Bae K, Jeong SW, Yoon KA, Yoon HY, Do SH, Kim B, Kim JH (2022): Adjuvant therapy with imatinib for an incompletely resected multilobular tumour of bone in a dog. Vet Med-Czech 67, 590–597.

Abstract: A 5-year-old neutered male Shiba Inu dog presented with a history of oral bleeding, dysphagia, and depression for 3 weeks. The physical examination revealed a firm mass in the right caudal palatal region along the level of PM4–M2. On the computed tomography, the mass was round-to-oval in shape and 22 mm × 30 mm × 15 mm in size. The mass contained multiple bone attenuated materials with a palatal bone lysis of 4 mm × 6 mm. A complete resection of the mass was proposed; however, the owner declined due to the risk of complications associated with the radical surgery. Therefore, a palliative resection and biopsy of the mass were performed. On the histological examination, the mass was diagnosed as grade 2 multilobular tumour of bone (MTB). Since the mass was incompletely resected, adjuvant therapy was pursued along with targeted therapy using a tyrosine kinase inhibitor. The tumour cells showed overexpression of the receptor of tyrosine kinase for c-KIT, PDGFR-α, PDGFR-β, and FGFR1 compared to normal tissue cells. Additionally, the cytotoxic effect of imatinib on the MTB cells was confirmed *in vitro*. Four weeks postoperatively, the administration of imatinib and carprofen was initiated and continued for 259 days. The patient maintained a good functional outcome for 306 days after the initial presentation.

Keywords: canine; carprofen; sarcoma; target therapy; tyrosine kinase inhibitor

Canine multilobular tumour of bone (MTB) is an uncommon bone-derived tumour that occurs mainly in the flat bones of the skull, more specifically in the maxilla, mandible, and calvarium (Banks and Straw 2004). Other locations of occurrence include the zygomatic arch, tympanic bulla,

Supported by the Konkuk University Premier Research Fund in 2020 (KU2019-A019-0584). The funder had no role in the design of the study; collection, analysis, and interpretation of data; and writing of the manuscript.

https://doi.org/10.17221/85/2021-VETMED

os penis, hard palate, ribs, and pelvis (Straw et al. 1989; Dernell et al. 1998; Cook et al. 2017). MTB is a fixed and firm tumour which arises from bone tissue protruding into the adjacent cavitary spaces, such as the oronasal, pharyngolaryngeal or endocranial cavities, with a unique histological multilobulated pattern and lobulated "popcorn ball" on imaging (Banks and Straw 2004). The clinical signs of MTB are mainly caused by the compression of the surrounding tissues rather than the tumour itself. Reported clinical signs include pain, neurological signs, orbital signs, ingestion disorders, and respiratory disorders, depending on the compression of the adjacent tissues (Banks and Straw 2004).

In veterinary medicine, an effective strategy to treat MTB is its complete resection with safety margins. However, resection of a mass located in the caudal maxilla is often technically challenging, and a poor postoperative prognosis has been reported, especially when the tumour extends past the palatal midline (Tuohy et al. 2019; Nakahara et al. 2020). Although several successful resections of caudal maxillary tumours have been reported, the necessity of extensive reconstruction surgery and high complication rates related to the surgery have also been reported (MacLellan et al. 2018; Tuohy et al. 2019; Nakahara et al. 2020).

Despite being reported in several studies, the efficacy of adjuvant radiotherapy and chemotherapy for MTB remains unclear (Dernell et al. 1998). Recently, tyrosine kinase inhibitors (TKIs) have been increasingly used in veterinary patients with cancer (London 2009). Receptor tyrosine kinases (RTKs) are important regulators of intercellular communication, controlling cell growth, proliferation, differentiation, survival, and metabolism (Zwick et al. 2002). Constitutive activation and/or overexpression of RTKs induces persistent signal transmission pathways that cause unregulated cell growth and tumoral proliferation (London 2009). TKIs inhibit RTK by blocking the ATP-binding site of the kinases which disrupt the phosphorylation of the kinases and initiation of the intracellular signal cascade (London 2009).

Imatinib is a small TKI molecule designed to specifically target the constitutively activated Bcr-Abl tyrosine kinase in human chronic myelogenous leukaemia (CML) (London 2009). Imatinib inactivates the Bcr-Abl tyrosine kinase and has been reported to have substantial clinical activity in the treatment of CML (Buchdunger et al. 2002; London 2009). Beyond the activity reported in the CML treatment, the inhibitory activity of imatinib has been reported in several tyrosine kinases, such as platelet-derived growth factor receptor (PDGFR)-α, PDGFR-β, and KIT (Buchdunger et al. 2002). The dysregulation of these tyrosine kinases has been reported in several tumours, such as mast cell tumour (MCT), gastrointestinal stromal tumour (GIST), and sarcomas. The clinical efficacy of imatinib to these tumours has also been reported in dogs (Buchdunger et al. 2002; London 2009; Kim and Kim 2018; Kim et al. 2018). However, there have been no reports on the clinical efficacy of imatinib as an adjuvant therapy after partial surgical resection of a palatal MTB.

Case description

A 5-year-old castrated male Shiba Inu presented with persistent oral bleeding, dysphagia, and depression for 3 weeks. The physical examination revealed an ulcerative firm mass protruding from the oral cavity, and it was positioned on the right caudal hard palate at the level of PM4 to M2 (Figure 1A). Additionally, an enlarged right mandibular lymph node was discovered on palpation, and an occasional wheezing sound related to a partial airway obstruction was observed on auscultation. The complete blood count testing revealed a decreased packed cell volume (35.1%, reference interval 37–55%), which may have resulted from the recent oral bleeding. The serum chemistry was unremarkable, except for an increase in the C-reactive protein level (219.1 nmol/l, reference interval 9.5–95.2 nmol/l). The computed tomography (CT) showed a round- to oval-shaped mass, 22 mm × 30 mm × 15 mm [width (W) × length (L) × height (H)] in size, adjacent to the palatal midline (Figure 2A) with a slightly irregular, but well-defined, margin and multiple bone attenuations suspected to be mineralisation. A palatal bone lysis of 4 mm × 6 mm (W × L) in size was revealed on the dorsal side of the mass. The right mandibular and retropharyngeal lymph nodes (RLNs) were enlarged.

For an accurate diagnosis, a mass resection and histopathological examination were indicated. The anatomical position of the tumour, which was close to the midline, indicated a bilateral caudal maxillectomy for safety margins. An additional biopsy of the enlarged regional lymph node for the assessment of metastatic change was also necessary. However,

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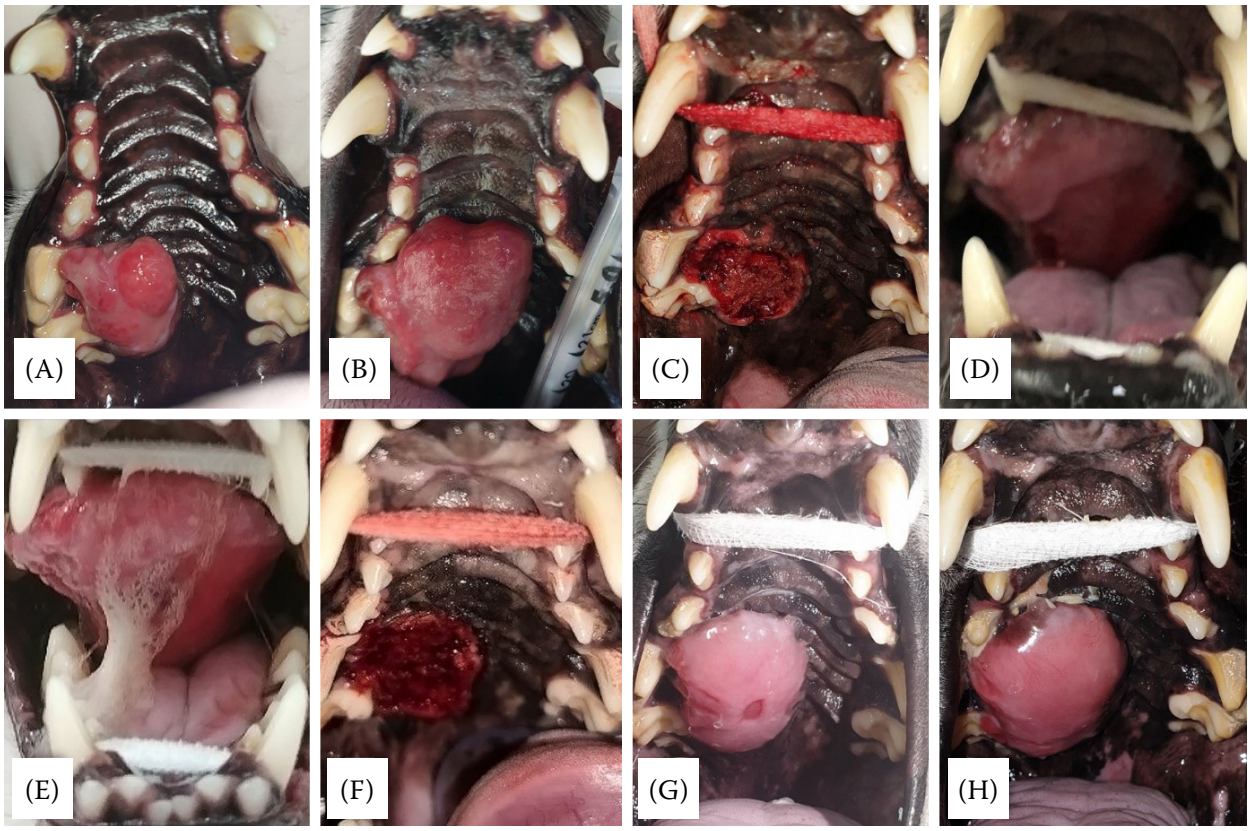

Figure 1. Clinical lesions in a dog with palatal MTB (multilobular tumour of bone)

(A) At presentation, the ulcerative mass is located on the right caudal palate at the level of PM4 to M2, adjacent to the palatal midline and soft palate. (B) Four weeks after the initial presentation, the mass has grown to over twice its initial size. (C) The gross lesion after the first resection of the mass in image (B). (D) Four weeks after the first surgery, the mass obstructs most of the oral cavity. At this point, the oral imatinib therapy is initiated. (E) At 8 weeks after the first surgery and 4 weeks after the initiation of imatinib, the entire obstruction of the oral cavity is revealed. (F) The second partial resection of the mass is performed 8 weeks after the first resection. (G) The gross lesion at 8 weeks after the second surgery and 12 weeks after the initiation of imatinib. (H) At 16 weeks after the second surgery, the size of the mass 20 weeks after commencing the imatinib treatment

the owner declined the option of a complete surgical resection due to the potential complications related to the radical surgery. At the owner's request, the dog was discharged with a prescription of the analgesic medication carprofen (Rimadyl; Zoetis, Lincoln, NE, USA) at 2.2 mg/kg by mouth (p.o.), twice a day for 7 days. Three weeks later, the dog developed dyspnoea and dysphagia due to the rapidly growing oral mass that was more than two times larger than before. A partial resection of the oral tumour was pursued to alleviate the clinical signs related to the obstruction of the oral cavity. The patient's owner refused the resection of the enlarged lymph nodes to diagnose any potential metastasis and wanted only the alleviation of the current problem associated with the tumour without any additional surgical procedure. For the induction and maintenance of the anaesthesia, propofol (Anepol injection; Hana Pharm. Co. Ltd., Seoul, Republic of Korea) and isoflurane (Ifran; Hana Pharm. Co. Ltd., Seoul, Republic of Korea) in oxygen were used. The tumour protruding into the oral cavity was identified and resected using a scalpel and monopolar electrocautery (Covidien; Norwalk, CT, USA; Figures 1B,C and 3A). Incomplete resection with gross residual tumour was performed because complete surgical excision was not possible, given the location and invasiveness of the tumour. The haemorrhaging from the hard palate was controlled with monopolar electrocautery and an absorbable gelatine sponge (Gelfoam; Pfizer, New York, NY, USA). Additionally, a normal tissue sample, 0.5 cm in diameter, was from the premaxilla obtained at a distance of more than 3 cm from the tumour and used

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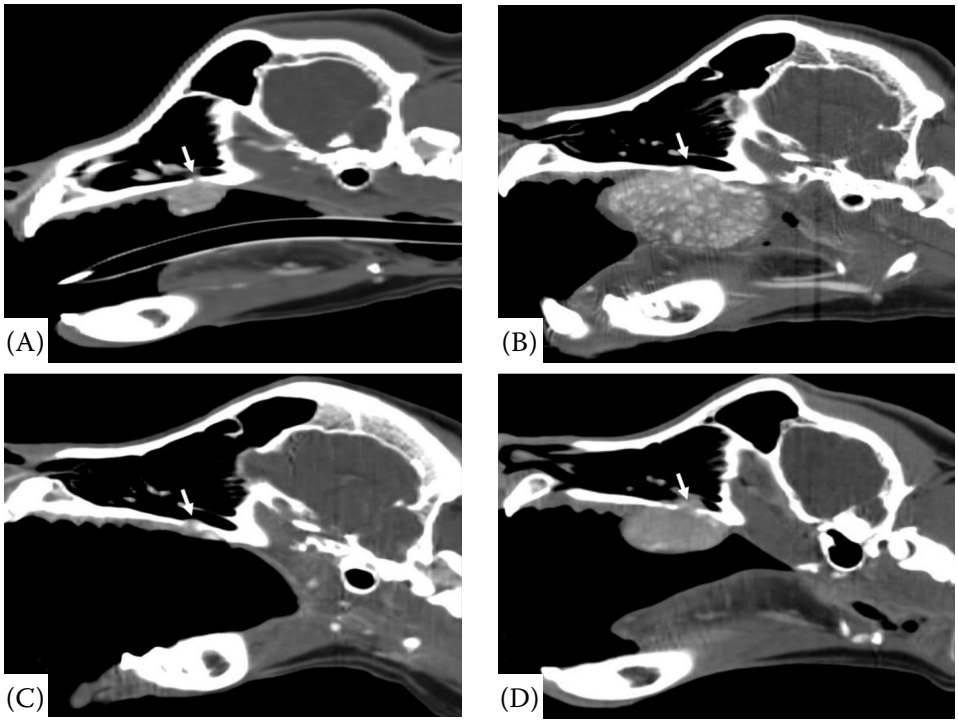

Figure 2. CT images of a dog diagnosed with palatal MTB

(A) On the day of presentation, the size of the mass measured 22 mm × 30 mm × 15 mm (W × L × H) and the maximum diameter of the bone lysis (arrow) of the palatine bone measured 4 mm × 6 mm (W × L). (B) At 8 weeks after the first resection and 4 weeks after commencing imatinib treatment, the size of mass measured 41 mm × 71 mm × 30 mm (W × L × H). The maximum diameter of the bone lysis (arrow) measured 8 mm × 7 mm (W × L). Note that a more lobular appearance and fine granular appearance is observed within the lobulations. (C) After the second partial resection of the mass in image (B), a mass was not detected. (D) At 16 weeks after the second resection and 20 weeks after commencing the imatinib treatment, the size of the mass measured 24 mm × 40 mm × 17 mm (W × L × H). The maximum diameter of the bone lysis (arrow) measured 9 mm × 12 mm (W × H)

H = height; L = length; MTB = multilobular tumour of bone; W = width

to compare the degree of expression of the RTKs between the normal and resected tumour cells.

The histological examination revealed that the tumour was an MTB appearing infiltrative regionally and heterogeneously in composition that included randomly distributed and lobulated islands (Figure 3B). These islands were variably comprised of mineralised bone, chondroid tissue, and hyaline cartilage interspersed among a stromal layer populated by spindle-shaped fibroblasts. The mitotic figures were less than one per 400 × field on average. The histological grade was determined as grade 2 according to a previous report regarding MTB (Dernell et al. 1998). After surgery, the patient's symptoms, including the dyspnoea and dysphagia, were instantly alleviated. Given the expected incomplete resection, the administration of TKI was determined to be an appropriate adjuvant therapy for this patient.

The total RNA was extracted from the surgically resected tumour and normal tissues using a TRIzol reagent and was reverse-transcribed into cDNA using a two-step reverse transcription polymerase chain reaction (PCR) kit (Invitrogen, Carlsbad, CA, USA). PCRs were run using reaction mixtures that contained a 10X PCR buffer, 2 µl of the template cDNA, 0.5 µM of gene-specific oligonucleotide primers, 0.2 mM of deoxyribonucleotide triphosphate, and 2.5 IU Taq DNA polymerase (Takara Bio Inc., Shiga, Japan). Amplifications were performed using a thermocycler (Bio-Rad, Hercules, CA, USA) as follows: 10 min at 95 °C, 28–30 cycles of denaturation-annealing-extension and 7 min at 72 °C. The PCR products were electrophoresed on 2% agarose gel and visualised under an ultraviolet (UV) transilluminator. After electrophoresis, images of the agarose gel were acquired and analysed using Image Lab Software (ChemiDoc XRS+

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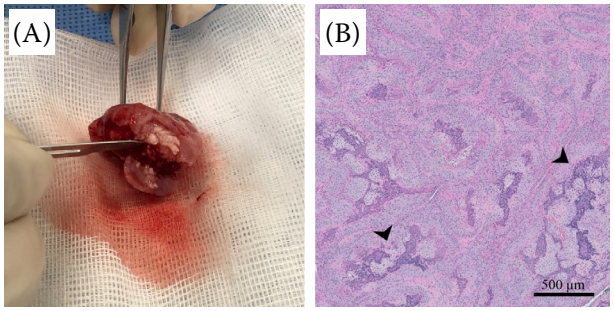

Figure 3. Oral mass gross morphological and histological features in a dog with palatal MTB (multilobular tumour of bone)

(A) At the gross level, the mass comprises multiple, variously sized mineralised materials surrounded by a fibrous septum. (B) Histopathology of the oral mass reveals that the tumour is heterogenous in composition and irregularly shaped, small to large, randomly distributed, and often comprising coalescing islands of variably well mineralised bound, chondroid tissue, and hyaline cartilage interspersed among a fibrocellular stroma, with bundled collagen populated by plump spindle shaped fibroblasts (arrow heads). Haematoxylin and eosin (H&E) stain; magnification 50 ×; scale bar = 500 µm

imaging system; Bio-Rad, Hercules, CA, USA). Glyceraldehyde-3-phosphate dehydrogenase was used as the internal control to compare the expression levels of the target genes. We compared the mRNA expression levels of targetable RTK genes, including the vascular endothelial growth factor receptor-1 (VEGFR-1), VEGFR-2, platelet-derived growth factor receptors-α (PDGFR-α), PDGFR-β, B-RAF, epidermal growth factor receptor (EGFR), c-KIT, ErbB2 (EGFR2), and fibroblast growth factor receptor 1 (FGFR1), between the tumour and adjacent normal tissues collected from the patient. PDGFR-α, PDGFR-β, c-KIT, and FGFR1 were overexpressed in the tumour tissues compared to the normal tissues (Figure 4A). Based on the results of the RTK overexpression in the tumour cells, an anticancer drug sensitivity test was performed *in vitro*. Several selected TKIs and conventional anticancer medicines were tested, and imatinib showed to have the most potent anticancer effect on the tumour cells. Moreover, after confirming the cytotoxic effect of imatinib on the MTB cells

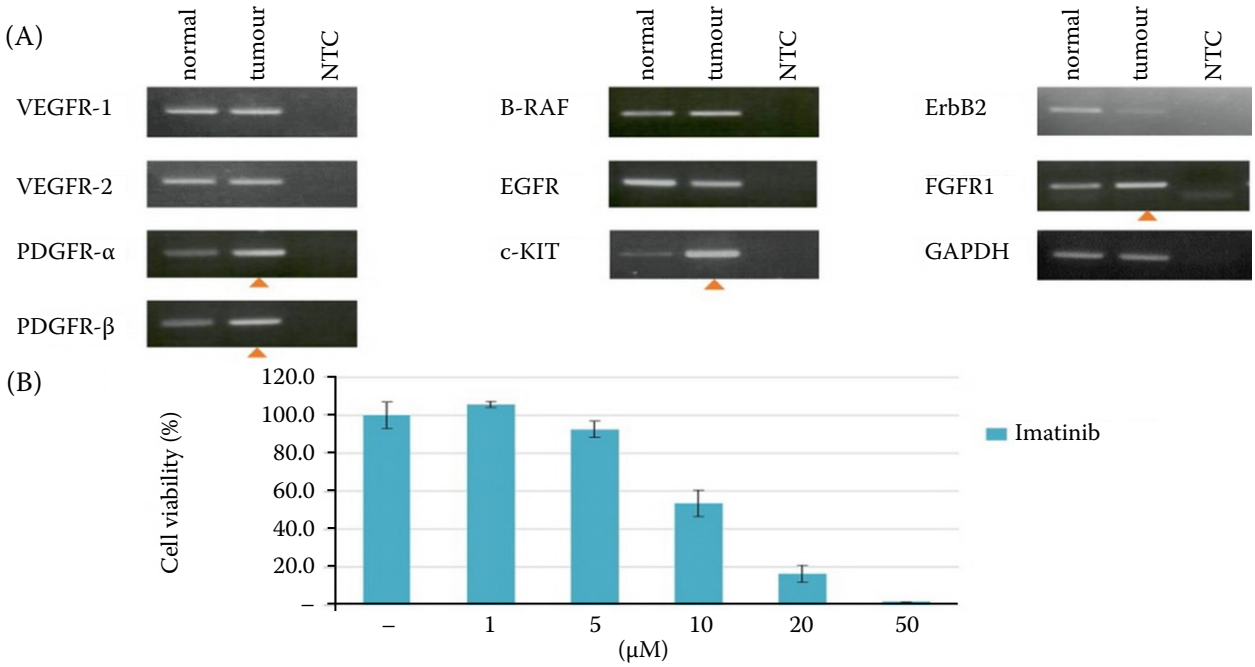

Figure 4. mRNA expression levels of various RTK genes and the cytotoxic effect of imatinib in the tumour cells attained from a dog with MTB

(A) mRNA expression of RTKs in the normal and tumour tissue samples from the present patient. Note that PDGFR-α, PDGFR-β, c-KIT, and FGFR1 are overexpressed (arrowheads) in the tumour compared with the normal tissues. (B) The cytotoxic effect of imatinib on MTB cells *in vitro*. Note that the concentration of imatinib is observed as 10 µM through application in the MTB cell culture. GAPDH was used as the internal control

EGFR = epidermal growth factor receptor; FGFR1 = fibroblast growth factor receptor 1; GAPDH = glyceraldehyde-3-phosphate dehydrogenase; MTB = multilobular tumour of bone; NTC = negative control; PDGFR = platelet-derived growth factor receptor; VEGFR = vascular endothelial growth factor receptor

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in vitro, an IC50 concentration of imatinib was observed at 10 μM during application on the MTB cell culture *in vitro* (Figure 4B).

Four weeks after surgery, the oral mass had rapidly regrown, and the patient's dysphagia reappeared (Figure 1D). At this time, 10 mg/kg/day of imatinib (Gleevec; Novartis, Basel, Switzerland) and 2.2 mg/kg/12 h of carprofen were also administered. Approximately 4 weeks after the imatinib administration, the growth rate of the tumour decreased (Figure 1E). However, the tumour was sufficiently large enough to obstruct the entire oral cavity, and a second surgical resection of the tumour was performed similar to the first resection (Figure 1F).

The CT showed the mass re-obstructing the entire oral cavity, and the soft palate was compressed by the mass. The size of the mass was 41 mm × 71 mm × 30 mm (W × L × H), and the palatal bone lysis increased to 8 mm × 7 mm (W × L; Figure 2B,C).

The right mandibular lymph nodes and RLN were nearly twice the size of the lymph nodes detected on the first CT scan. The imatinib administration was discontinued for 1 day before surgery and re-administered on the 5th day after surgery. The delay in the growth of the mass was clearly shown on routine rechecks 16 weeks after the second surgery (Figure 1G,H).

For 16 weeks after the second surgical resection, the tumour grew to 24 mm × 40 mm × 17 mm in size, which was 19% of the maximum growth of the tumour after the first surgical resection (Figure 2D).

There was no significant change in the enlarged lymph nodes compared to that in the previous CT scan. The owner requested an additional surgical resection of the tumour as a preventive measure. The additional surgical resection was performed similar to the first and second surgeries. The surgical bleeding from the resected tumour was easily controlled compared to the surgical bleeding in the previous surgeries. The imatinib and carprofen administration was continued after the surgery. The patient was followed up for 306 days (44 weeks) after the first presentation, where adverse effects related to imatinib and carprofen administration were not detected on the regular checks that included physical and blood examinations. All the samples were collected under the approval of the Institutional Animal Care and Use Committee (KU19189) and after the owner's consent was obtained.

DISCUSSION AND CONCLUSIONS

A canine MTB is a bone-derived tumour that is locally invasive and moderately metastatic (Dernell et al. 1998; Banks and Straw 2004). Considering the high occurrence rates of MTB in the skull and their locally invasive features, clinical signs are associated with compression and lysis of the surrounding cranial organs. The clinical signs in the present patient included persistent oral bleeding, dysphagia, and respiratory distress due to the presence of a mass on the caudal part of the hard palate. Generally, MTB is reported to be a slow-growing tumour, although the rapid growth of MTB has recently been reported in a young dog in which the tumour recurred 8 days after the surgical resection (Cook et al. 2017). In that study, the rapid growth of MTB suggested a malignant transformation of the tumour (Cook et al. 2017). In the present case, the tumour had a relatively rapid growth rate, and the caudal palatal position of the tumour worsened the clinical signs.

The treatment recommendation for MTB is the complete surgical resection with a wide margin (Straw et al. 1989; Dernell et al. 1998). However, for tumours in the caudal hard palate, surgical resection is often challenging as finding the tumour and clinical signs are difficult before the tumour grows to a large size (Banks and Straw 2004). In a previous report, the occurrence of a tumour caudal to PM3 of the maxilla was associated with a 4.3 times higher mortality rate than that of a tumour cranial to PM3 (Lascelles et al. 2003). Limited surgical sites and intraoperative complications, such as anaemia and hypotension related to the highly vascularised features of the caudal maxilla, have also been reported in surgical procedures (MacLellan et al. 2018).

In the present case, the tumour was located along the PM3–M2 level and close to the midline of the hard palate. Considering the tumour size and location, the owner declined the radical surgical procedure and instead chose palliative surgery to resolve the pharyngeal obstruction and related clinical signs and adjuvant therapy to control the distant metastasis and quality of life. The right mandibular and RLN enlargements on the CT scans suggested potential metastasis. An excisional biopsy of the enlarged lymph nodes was needed to diagnose the metastasis and predict the prognosis. The owner refused to grant permission to perform the lymph nodes dissection, which required an additional surgical procedure. The CT scan revealed

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no change in the size of the lymph nodes after administering imatinib with carprofen. However, the inability to accurately evaluate the lymph node metastasis is a diagnostic limitation of this case.

In the present case, the gene expression, such as c-KIT, PDGFR-α, PDGFR-β, and FGFR1, was increased in the MTB cells than that in normal tissue cells. The overexpression of the RTKs by these genes can cause malignant transformation by the dysregulation of the intercellular communication controlling the cell growth, proliferation, differentiation, survival, and metabolism (Zwick et al. 2002). Imatinib targets PDGFR-α, PDGFR-β, and KIT (London 2009). The clinical efficacy of imatinib targeting these RTKs was revealed during the treatment of several tumours, such as MCT, GIST and sarcomas in dogs (Buchdunger et al. 2002; Kim and Kim 2018; Kim et al. 2018).

The expression of platelet derived growth factors (PDGFs) by binding to platelet derived growth factor receptors (PDGFRs) has been linked to the malignant transformation of cells and it promotes tumour angiogenesis and autocrine stimulation of the tumour cells (Buchdunger et al. 2002). PDGF acts as a mitogen for the endothelial cells and induces the autocrine loop of the vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) (Buchdunger et al. 2002). Imatinib inhibits tumour angiogenesis by inactivating the angiogenic effects of PDGFR and this antiangiogenic activity prevents growth of tumour cells.

In this case, we performed serial surgical resections for palliative purpose. After the imatinib administration in the patient, the surgical bleeding during the resection of the tumour and tumour cell growth were decreased. The antiangiogenic effect of imatinib by inactivating the PDGFRs may decrease the angiogenesis of the MTB cells. The interstitial fluid pressure (IFP) in tumour cells is also increased by the PDGF expression (Buchdunger et al. 2002). Increased IFP occurs in a solid tumour with a diminished hydrostatic gradient from the capillary to the interstitium (Buchdunger et al. 2002). A diminished hydrostatic gradient could depress the anticancer agent delivery to the tumour cells (Buchdunger et al. 2002). After the administration of imatinib, the tumour growth rate decreased in the present case. This suggested that the clinical uptake of imatinib in MTB cells was increased by decreasing the IFP through inactivating the PDGFR.

The c-KIT overexpression was also confirmed by the mRNA expression by comparing the MTB cells with the normal tissue. The overexpression and mutation of the c-KIT gene can induce malignant transformation by the constitutively activated KIT, which regulates the differentiation and survival in cells (Buchdunger et al. 2002; Zwick et al. 2002; London 2009). Imatinib inhibits indiscriminate cell proliferation in tumours through the inhibition of KIT autophosphorylation (Buchdunger et al. 2002). The clinical efficacy of imatinib to several tumour, such as MCT, GIST, and melanoma, was reported through the inactivation of KIT in these tumour cells which have aberrant expression of c-KIT (Bonkobara 2015).

In the present case, the inhibitory effect of imatinib in the MTB could be predicted based on the result of the cytotoxic effect of imatinib on the MTB cells. In consideration of the *in vitro* biochemical laboratory results of the MTB cells and imatinib inhibitory effects on these RTKs, the clinical efficacy of imatinib on the MTB cells could be suspected by targeting PDGFR-α, PDGFR-β, and KIT in the MTB.

Carprofen is a non-steroidal anti-inflammatory drug (NSAID) that reduces inflammation by the inhibition of cyclooxygenases (COXs)-1 and -2. The anti-tumour effect of NSAIDs has been reported in human malignancies (Wolfesberger et al. 2006). For instance, the inhibition of overexpressed COX-2 in cancer cells is suggested to be an effective approach to treat several types of cancer (Wolfesberger et al. 2006; Poradowski and Obminska-Mrukowicz 2019).

In previous reports, the inhibitory effects on canine osteosarcoma cellular growth *in vitro* were confirmed by use of meloxicam or carprofen (Wolfesberger et al. 2006; Poradowski and Obminska-Mrukowicz 2019). Although in the present case, carprofen was administered for palliative purposes to reduce the pain and inflammation associated with tumours, the potential effect of carprofen on delaying the growth of MTB was not excluded. However, the effect of carprofen on delaying the MTB growth may be excluded as the prescription of carprofen before imatinib only reduced the pain, not the tumour growth. In addition, so far, the clinical effects of NSAIDs on MTB have not been reported.

The toxic effects of imatinib administration in dogs have been reported as either non-clinical or resolvable by the transient withdrawal of imatinib (Bonkobara 2015). The toxic effects included mild vomiting, neutropenia, hepatotoxicity, and

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nephrotoxicity in several reports (Isotani et al. 2008; Bonkobara 2015). The patient tolerated a dose of 10 mg/kg/day p.o. for approximately 37 weeks, and no adverse effects were observed. Due to the adverse effect of imatinib on the wound healing postoperatively, the timing of the imatinib cessation is important. In cases of human metastatic GIST, imatinib administration could be terminated a day before surgery and resumed within 2 weeks after surgery without interruption to the wound healing (Barnes et al. 2005). However, in this case, imatinib was discontinued from 1 day preoperatively to 5 days postoperatively for the second surgery because the early resumption of imatinib after surgery is thought to maximise the effect of the palliative surgery.

In conclusion, imatinib and the NSAID therapy may slow the growth of canine MTB in cases where wide resection is difficult as it can help relieve any clinical signs associated with a tumour invasion to adjacent organs. In the future, large-scale studies of the efficacy of TKIs against MTB are needed for veterinary patients.

Conflict of interest

The authors declare no conflict of interest.

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Received: June 21, 2021
Accepted: May 13, 2022
Published online: August 19, 2022