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Effective palliative treatment of recurrent soft tissue sarcoma in a dog using imatinib mesylate (Gleevec®)

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Abstract: A 14-year-old neutered female Yorkshire terrier presented with a rapidly growing gluteal mass. There was a history of surgical resection of a mass diagnosed as a grade two soft tissue sarcoma in the same region a year earlier. The second mass was surgically excised and histopathologically diagnosed as grade two soft tissue sarcoma. A further relapse occurred six months after the second surgery. On that occasion, the dog was treated with metronomic chemotherapy consisting of cyclophosphamide and piroxicam, which failed to adequately control the disease and the mass increased 2.5-fold in size in three weeks. Imatinib treatment was started, after which there was a 62% reduction in the size of the mass. The patient has remained in partial remission for five months. To the authors' knowledge, this is the first report on the use of imatinib to treat canine soft tissue sarcoma. Imatinib might be a useful treatment for soft tissue sarcoma that recurs after surgical resection.

Keywords: canine; subcutaneous tumours; target therapy; tyrosine kinase inhibitor

Soft tissue sarcoma (STS) is a tumour that develops from tissues of mesenchymal origin and can occur at almost any anatomic site (Ettinger 2003; Bray 2016). These tumours usually develop in the subcutaneous tissues and are estimated to comprise 15% of all skin neoplasia in dogs (Liptak and Forrest 2013). In veterinary medicine, the most effective strategy for STS is surgery, and radiotherapy and chemotherapy are now being considered as adjuvant treatments (Stefanello et al. 2008; Bray 2016). Neoadjuvant chemotherapy, in which chemotherapy is administered before surgical resection, is not a well-accepted protocol in dogs (Bray 2017). Furthermore, better tissue penetration can be achieved because the microvasculature has not been disrupted by surgery (Gortzak et al. 2001; Hohenberger and Wysocki 2008; Fujiki et al. 2011; Bray 2017). Recently, Elmslie et al. (2008) reported that metronomic therapy effectively delayed tumour recurrence in dogs with incompletely resected STS. However, there are no clinical studies to suggest that adjuvant use of a tyrosine kinase inhibitor (TKI) has any beneficial impact on outcomes or surgical margins in dogs with STS.

Imatinib mesylate (Gleevec®; Novartis) is an inhibitor of the tyrosine kinase receptor that autophosphorylates and phosphorylates other proteins on tyrosine residues (Shchemelinin et al. 2006). In dogs with STS, autocrine loops of growth factor stimulation by expression of platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) have been documented, suggesting that TKI-mediated inhibition of such autocrine loops may promote regression of metastatic disease (London et al. 2003). However, there are no reports on the use of TKIs as adjuvants for postoperative recurrence of STS. This case report describes the use of a TKI for recurrent STS after multiple surgical resections in a dog that was not responsive to palliative metronomic chemotherapy.

Case description

A 14-year-old neutered female Yorkshire terrier presented with a gluteal mass that had grown rapidly in the previous month. One year earlier, a mass had been surgically excised from the same region and histopathologically diagnosed as STS.

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The recurrent mass measured 1.5 × 2.0 cm and was solid and mobile. The only other abnormality on physical examination was intermittent coughing. The dog weighed 2.6 kg, had a pulse of 132 per minute, a respiratory rate of 20 breaths per minute and a rectal temperature of 38.1 °C. The mucous membranes were pink and the capillary refill time was normal as were direct and consensual pupillary light reflexes. A complete blood count was also normal, and serum chemistry was unremarkable except for a mild increase in blood urea nitrogen (11.42 mmol/l, reference interval 2.5–9.64 mmol/l).

The recurrent mass was removed at a second surgery with approximately 2-cm margins, and histopathology showed a loosely cellular neoplastic lesion, within which the neoplastic cells were haphazardly arranged in short interlacing bundles and streams (Figure 1). The neoplastic cells had distinct cell margins and contained eosinophilic fibrillar cytoplasm and elongated to oval nuclei. Large multi-focal areas of the lesion were necrotic and comprised up to 5% of the total neoplastic cell area. The neoplastic cells were spindle-shaped to stellate-shaped and contained finely- to coarsely-stippled chromatin. The mitotic count was seven per 10 high-power fields. Neoplastic cells were excised with peripheral and deep margins of 3.8 mm and 1.9 mm, respectively. The histopathological diagnosis was STS, grade two. No additional treatment was offered postoperatively.

Six months after the second surgery, a solid mass (1.1 × 1.2 cm in diameter) was again noted in the gluteal region. Serum chemistry revealed a mild increase in blood urea nitrogen (30 mg/dl). Thoracic radiography revealed cardiomegaly (Vertebral Heart Score 11.3) and tracheal collapse (grade 4/4), but no pulmonary metastasis. A peak tricuspid regurgitant jet velocity of 3.2 m/s was detected on spectral Doppler echocardiography. A diagnosis of tracheal collapse with systolic pulmonary arterial hypertension (45.96 mm Hg) was made. On the basis of the cardiac diagnosis, 0.5 mg/kg of furosemide (Lasix®; Handok Pharmaceuticals Co., Seoul, Republic of Korea), 1 mg/kg of spironolactone (Spilacton®; Daewon Pharm., Seoul, Republic of Korea) and 2 mg/kg of sildenafil (Viagra®; Pfizer, Seoul, Republic of Korea) were initiated twice daily by mouth.

On the basis of the similar gross appearance, aspiration cytology and anatomical location, the gluteal mass was assumed to be a recurrence of STS. At this time, the owners declined the offer of a biopsy. Instead of further surgery, metronomic chemotherapy comprising 10 mg/m^2 of cyclophosphamide (Alkyloxan Tab.; JW Pharmaceutical Co., Seoul, Republic of Korea) and 0.3 mg/kg of piroxicam (Piroxicam Cap; Crown Pharmaceutical Co.,

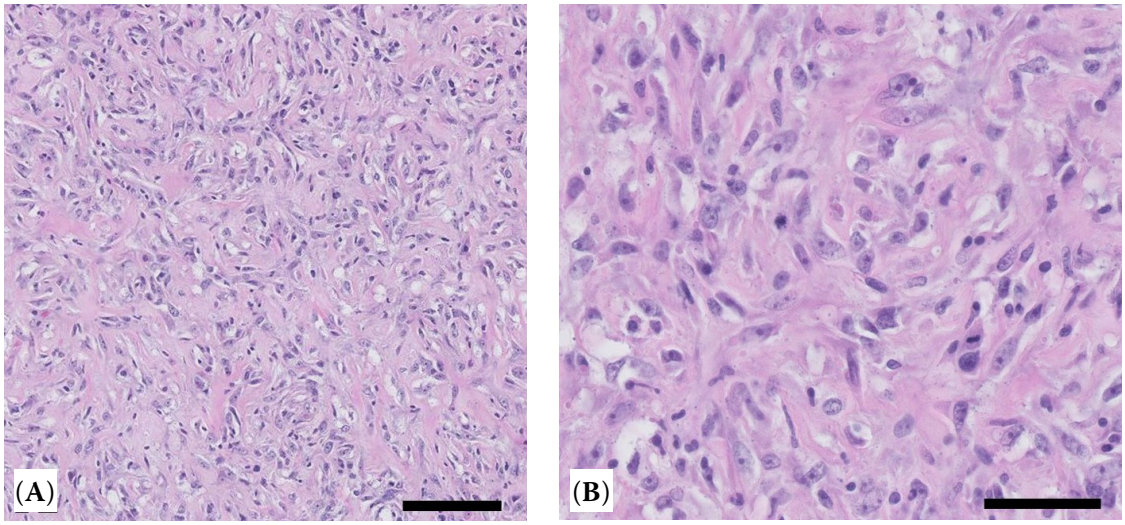

Figure 1. Histological section of the gluteal mass. (**A**) The neoplasm is composed of spindle-shaped to stellate-shaped cells that are haphazardly arranged in short interlacing bundles and streams. The neoplastic cells are often separated by a small amount of collagenous matrix. Haematoxylin-eosin staining, × 100 objective. (**B**) The neoplastic cells have distinct cell borders, eosinophilic fibrillar cytoplasm and elongated-to-oval nuclei. The nuclei have finely- to coarsely-stippled chromatin and two or three variably distinct nucleoli. Marked anisocytosis and anisokaryosis are seen. Haematoxylin-eosin staining, × 400 objective

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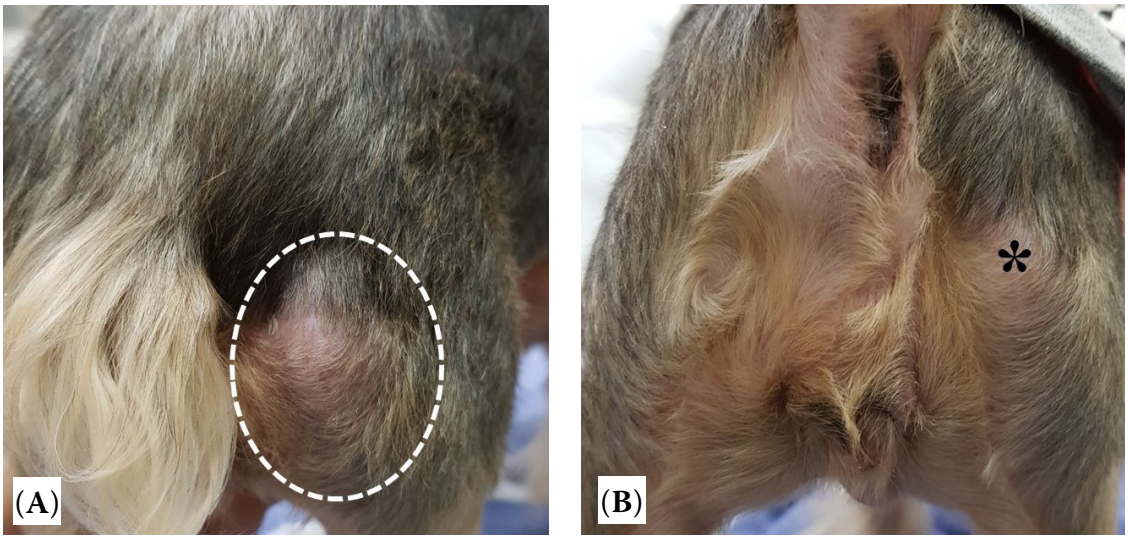

Figure 2. (**A**) A solid mobile mass (dashed circle) can be seen in in the gluteal region at the time of the second relapse. (**B**) One week after imatinib therapy, the mass (*) has decreased in size

Seoul, Republic of Korea) was started daily by mouth. However, by three weeks later the mass had increased 2.5-fold in size (to 1.9 × 3.0 cm in diameter; Figure 2A). Cyclophosphamide and piroxicam were discontinued and 10 mg/kg/day of imatinib (Gleevec®; Novartis, Basel, Switzerland) by mouth was started. One week later, the dog re-presented for a routine check, at which time the mass had decreased in size by 40% to 1.53 × 1.66 cm. After about 50 days of imatinib therapy, the mass was soft and had decreased by 62% to 0.5 × 1.06 cm, indicating a sustained partial response (Figure 2B). The dog experienced no side effects and laboratory investigations at this time revealed no abnormalities. The daily size change is shown in Figure 3. At follow-up five months later, all laboratory parameters, blood pressure, and physical examination were unremarkable and the mass remained in partial remission.

DISCUSSION AND CONCLUSIONS

STS is a common tumour in companion animals that has an incidence rate of 35/100 000 dogs/year and is estimated to comprise 15% of all skin and subcutaneous tumours in canines (Dorn 1976; Theilen and Madewell 1979). STS usually develops in a subcutaneous location (Liptak and Forrest 2013), grows slowly and tends to be unnoticed by the owner until it has reached a considerable size. Therefore, dogs with STS tend to present late. Clinical signs in dogs with STS may be associated with the anatomical location; however, in most cases, a palpable mass is the only clinical sign (Bray 2016). When part of the tumour is devitalised or has grown rapidly, the skin may no longer be able to accommodate the mass, and ulceration ensues (Liptak and Forrest 2013). The dog may present with a history of localised areas of inflammation and necrotic tissue (Bray 2016). The most common management strategy for STS in veterinary medicine is surgery (Dernell et al. 1998), and radiotherapy and chemotherapy are now being considered as adjuvant treatments (Forrest et al. 2000; Mutsaers 2009). For palliative care, radiotherapy can be used alone without surgery (Liptak and Forrest 2013), but the role of chemotherapy in

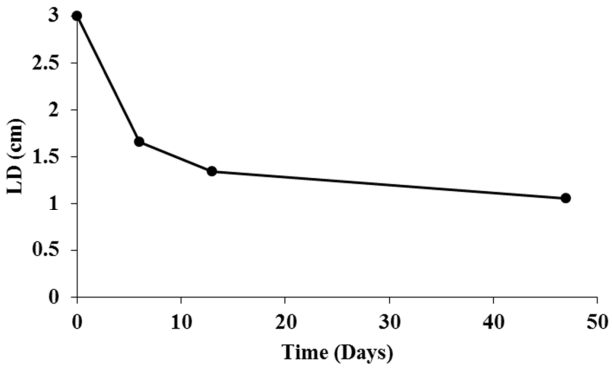

Figure 3. Change of gluteal mass size in a dog with soft tissue sarcoma. One week after commencement of imatinib (10 mg/kg, *p.o.*, *s.i.d.*) therapy, mass size is significantly reduced. Forty-seven days later, the mass has become soft and has further decreased in size
LD = longest diameter

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the management of dogs with STS is not yet defined (Liptak and Forrest 2013). In some countries, including Republic of Korea, radiotherapy is not available because of a lack of the necessary equipment and experienced operators. In these countries, there is no treatment option for dogs with STS that cannot undergo surgery. Medical treatment may be the only option in these patients. However, the response to high-dose chemotherapy is unpredictable and often only palliative, and the drugs used have a narrow therapeutic index (Arora and Scholar 2005). Metronomic chemotherapy with cyclophosphamide and piroxicam has been used as an adjuvant treatment in dogs with incompletely resected STS (Elmslie et al. 2008) and has been very effective in preventing recurrences. In the present case, the STS recurred after multiple surgical resections. As a palliative treatment, metronomic chemotherapy was used first but was ineffective. Subsequent targeted adjuvant therapy using a TKI has achieved partial remission for five months so far.

Modern targeted therapies elicit reduced levels of nonspecific toxicity (Arora and Scholar 2005) and target cancer-specific molecules and signalling pathways (Arora and Scholar 2005). One of the most important targets are the receptor tyrosine kinases, which have an important role in modulation of growth factor signalling (Arora and Scholar 2005). Tyrosine kinases autophosphorylate and phosphorylate other proteins on tyrosine residues (London 2009). Although there are several targeting strategies for protein kinases, the small-molecule TKIs have been the most effective to date. There is limited information on the clinical efficacy of the TKIs in the veterinary literature, because the therapeutic targets for most canine and feline cancers are not clearly defined (London 2009). Moreover, many of the TKIs used in human medicine are relatively expensive, which limits their use (London 2009). The first investigation of a TKI in veterinary medicine was a Phase I trial exploring the safety and efficacy of Palladia (SU11654), a novel multitargeted TKI (London 2003). In that study, partial responses occurred in two of four dogs with spontaneously occurring tumours, indicating an overall response rate of 50% (London 2003). These agents typically act as reversible or irreversible competitive inhibitors, essentially blocking the ATP binding site of kinases (London 2009).

Imatinib has been used recently to treat cancers in dogs and cats, particularly mast cell tumours (London 2009). Imatinib inhibits the tyrosine kinase receptor (London 2003) and was the first effective systemic treatment for gastrointestinal stromal tumours in humans (Stroobants et al. 2003). Imatinib competitively inhibits the split kinase family of tyrosine kinase receptors, including Kit, Abl and PDGF, which are dysregulated in several human and canine cancers (London 2009). Imatinib specifically inhibits the Bcr-Abl tyrosine kinase protein and is a selective inhibitor of the PDGF receptor, the gene for the Abl-related protein and Kit but is not an inhibitor of cytoplasmic tyrosine kinases or other receptors (Buchdunger et al. 2002). PDGF may have a role as a direct mitogen in endothelial cells, but also induces expression of VEGF in endothelial cells, which in turn causes an autocrine loop via stimulation of VEGF receptors (Buchdunger et al. 2002). PDGF may indirectly support formation of blood vessels via paracrine stimulation, given that PDGF-responsive stromal and perivascular cells are major sources of VEGF (Buchdunger et al. 2002). Furthermore, angiogenesis is influenced by PDGF via stimulation of vascular smooth muscle cells and recruitment of pericytes (Buchdunger et al. 2002). Imatinib also inhibits VEGF and basic fibroblast growth factor-stimulated vascularisation of subcutaneous implants in a mouse model of growth factor-induced angiogenesis (Buchdunger et al. 2002). VEGF is highly expressed in most high-grade STS in humans (Chao et al. 2001). Furthermore, in dogs with STS, expression of PDGF and VEGF resulting in autocrine loops of growth factor stimulation has been documented (London 2003). Therefore, inhibition of such autocrine loops may result in regression of metastatic disease in dogs with STS, as in the present case (London 2003).

This case report documents that use of imatinib achieved a partial response in a dog with recurrent STS that was not responsive to surgery and metronomic chemotherapy. Imatinib might be a feasible option for STS that recurs after surgery in dogs. Large-scale studies of the expression of angiogenic factors and the efficacy of TKIs in STS in veterinary medicine are now needed.

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