Long-term survival in a cat with pancreatic adenocarcinoma treated with surgical resection and toceranib phosphate

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Abstract

Case summary Primary pancreatic adenocarcinoma is an uncommon neoplasm seen in cats and often has a poor prognosis. We report a case of an 8-year-old male neutered domestic shorthair cat weighing 5.8 kg diagnosed with pancreatic adenocarcinoma treated with surgical resection and toceranib phosphate, which had a progression-free interval of 1148 days and survived for more than 1436 days. The treatment was well tolerated; however, the cat developed generalised coat hypopigmentation.

Relevance and novel information To our knowledge, the cat in our report has the longest progression-free interval and survival time post-surgical resection of pancreatic carcinoma treated with toceranib. Hypopigmentation as a side effect of toceranib has been reported in dogs, but this is the first case reported in cats.

Keywords: Toceranib phosphate; pancreatic carcinoma; chemotherapy; hypopigmentation

Case description

An 8-year-old male neutered domestic shorthair cat weighing 5.8 kg presented to the Small Animal Specialist Hospital (North Ryde) emergency department for lethargy and having vomited 2 h after a meal. There was no recent history of illness, dietary indiscretion or diet change.

On physical examination the cat was dull, tachycardic with a heart rate of 220 beats per min, had abdominal pain and a rectal temperature of 40ºC. Bloodwork was performed, which revealed neutropenia 0.09×10^9/l (reference interval [RI] $1.48–10.29 \times 10^9$/l), hyperglycaemia 10.2 mmol/l (RI 3.95–8.84 mmol/l), total calcium 1.94 mmol/l (RI 1.95–2.83 mmol/l), alkaline phosphatase 10 U/l (RI 14–111 U/l), pH 7.43 (RI 7.24–7.4), HCO_3 20.4 mmol/l (RI 22–24 mmol/l), PCO_2 33 mmHg (RI 34–38 mmHg) and K^+ 3 mmol/l (RI 3.5–5.8 mmol/l). A rapid immunomigration test for the detection of feline leukaemia virus antigen and feline immunodeficiency virus antibody was negative.

An abdominal-focused assessment with ultrasonography for trauma scan showed scant free abdominal fluid and a bright mesentery. Orthogonal abdominal radiographs were unremarkable. The patient was treated supportively with intravenous fluids and buprenorphine (0.02 mg/kg SC q8h) overnight. There was concern that the patient was developing systemic inflammatory response syndrome due to persistent pyrexia and tachycardia, and an abdominal ultrasound was recommended to screen for a source of infection.

On day 2 of hospitalisation the cat's temperature had normalised to 38.8ºC. A full abdominal ultrasound was performed, which revealed a trace amount of anechoic fluid – an irregular, complex echogenicity mass measuring 23×15 mm between the spleen and the kidney with two hypoechoic spherical structures adjacent to it measuring 7×11 mm in diameter. The mesentery in the region of the mass was hypoechoic. Ultrasound-guided fine-needle

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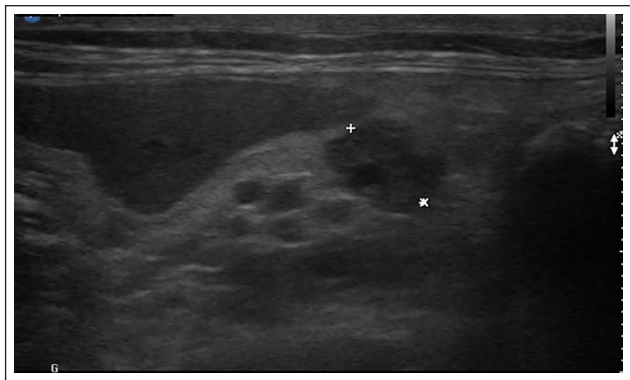Email: johanna.todd@sashvets.com

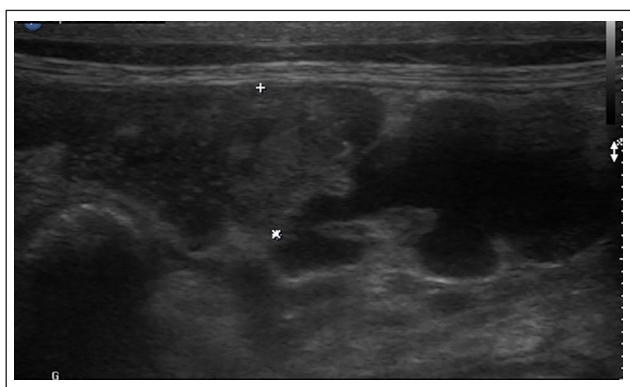**Figure 1** Ultrasound image of the pancreas

Figure 2 Ultrasound image of the pancreas

aspiration of the mass was performed and submitted for cytology. Aspiration of the hypoechoic structures revealed purulent material, which was submitted for culture and susceptibility. An in-house cytology review of the purulent material revealed intra- and extracellular rods, and treatment with marbofloxacin was initiated at 2mg/kg q24h PO and amoxicillin (20mg/kg IV q8h).

On day 3 of hospitalisation, the cat had developed a grade III/VI parasternal systolic heart murmur and was comfortable on abdominal palpation with suspicion for a mass effect in the right cranial abdomen. Repeat abdominal ultrasound identified a mass in the caudal aspect of the left pancreatic limb measuring 1.1×2.1 cm, surrounded by thin-walled structures suggestive of fluid pockets (Figures 1 and 2)

The most likely differentials were pancreatic neoplasia, abscess, pancreatitis or granuloma. Repeat complete blood count showed a neutrophilia of 24×10^9/l (RI 1.48–10.9 $\times 10^9$/l) with a left shift and monocytosis 0.82×10^9/l (RI 0.05–0.67 $\times 10^9$/l). Supportive care was continued. Orthogonal thoracic radiographs were negative for changes suggestive of gross metastatic disease. Cytology of the mass revealed epithelial dysplasia with septic pyogranulomatous inflammation. Exploratory laparotomy was recommended.

Exploratory laparotomy and oesophageal feeding tube placement were performed on day 4. A partial pancreatectomy was performed. The liver contained a few small patches of grossly different coloured tissue, and there were multiple discrete flat lesions within the falciform ligament, so both were biopsied. All tissue samples were submitted for histopathology.

During the postoperative period the patient had an echocardiogram, which was unremarkable. Culture of the abdominal fluid revealed a Gram-negative anaerobic bacillus (*Bergeyella zoohelum*) and *Clostridium perfringens*, both of which are sensitive to marbofloxacin. Histopathology revealed pancreatic duct carcinoma with moderate pleiomorphism and tumour tissue extending into the surrounding mesentery, normal liver and multifocal mesenteric steatitis. The patient was discharged 3 days post-surgery with an oesophageal feeding plan, marbofloxacin and metronidazole.

Seven days post-discharge the patient presented for an oncology consultation. The cat was eating the resting energy requirement on its own and had recovered well from surgery. Treatment with toceranib phosphate (Palladia; Zoetis) 15mg (2.78mg/kg) every second day was initiated.

Four weeks after starting toceranib a grade 1 increase in alanine aminotransferase (ALT) occurred, which self-resolved. Restaging with thoracic radiographs and abdominal ultrasound performed by a board-certified radiologist was performed 12 months after initial diagnosis, which did not show any evidence of metastatic or recurrent disease.

Fourteen months after starting treatment the patient developed a generalised change in haircoat from black to grey (Figure 3). Six months later, at a routine check-up, the patient was found to have lost 600g (10% body weight). The patient had a drug holiday for 2 weeks and the toceranib was restarted at three times weekly (Monday, Wednesday, Friday).

The patient last underwent repeat staging with thoracic radiographs and abdominal ultrasound performed by a board-certified radiologist 38 months after diagnosis. At this time the patient did not have evidence of metastatic disease or recurrence, resulting in a progression-free interval of 1148 days. At the time of writing, the patient was known to be alive and well 1436 days after diagnosis and still being treated with toceranib.

Discussion

Pancreatic cancers are rare in veterinary patients, representing <0.5% of reported tumours in dogs and cats.[1] Primary pancreatic tumours in cats are usually of epithelial origin and both adenocarcinoma of the pancreatic ducts and acinar forms have been reported.[2] There is no known sex or breed predilection, and it is most commonly seen in middle-aged to older cats.[3,4]

Figure 3 Hypopigmentation of the patient's coat during toceranib treatment

Clinically, it can be very difficult to differentiate pancreatic cancer from pancreatitis.[2] Patients commonly present with a history of weight loss, anorexia, vomiting, abdominal pain, abdominal distension, abdominal effusion, abdominal mass and icterus.[2,4] Commonly reported haematological and biochemical abnormalities include leukocytosis, hyperglycaemia and increased ALT.[2]

Radiographic findings for pancreatic tumours include reduced serosal detail and a mass effect in the region of the pancreas.[3] Ultrasonographic changes overlap with pancreatitis such as hypoechogenicity of the pancreas, hyperechoic peripancreatic mesentery, peritoneal effusion, pancreatic enlargement, pancreatic or peripancreatic mass and bile duct dilation, as seen in this case.[3,5] Nodular hyperplasia is also seen in older animals, and it has been suggested that single pancreatic masses detected on ultrasound that exceed 2 cm in at least one dimension are more likely to be neoplasia rather than nodular hyperplasia.[3] Given that pancreatitis, nodular hyperplasia and neoplasia can all produce mass effects, fine-needle aspiration of masses or fluid is warranted.[5] Bennett et al reported that cytological evaluation can assist in the diagnosis of pancreatic neoplasia.[5]

Feline exocrine pancreatic carcinoma has a reported metastatic rate of 32–50%.[2,4] The most common sites for metastasis are the liver, peritoneum and local lymph nodes, small intestine and lungs.[2,4] Historically, the prognosis was thought to be grave, with reported cases dying or being euthanased shortly after diagnosis owing to rapid progression and metastasis detected at the time of diagnosis.[2] More recently, there have been reports of patients having more favourable outcomes and longer survival times if they received treatment. Linderman et al reported a longer survival time if cats underwent surgery (median survival time 165 days vs 30 days for those cats who did not have surgery), and chemotherapy (median survival time 165 days vs 7 days for cats that did not have chemotherapy).[4] The chemotherapy used included single-agent gemcitabine, carboplatin, mitoxantrone, gemcitabine combined with carboplatin, imatinib, toceranib and masitinib. The overall prognosis remained guarded in this study, with a median survival time of 97.5 days; however, three cats survived >12 months.

For nine cats without metastatic disease at diagnosis that underwent surgery, Nicoletti et al reported a median survival time of 316 days, with four cats living >12 months.[6] One cat survived 964 days. A variety of different chemotherapy protocols were used in the adjuvant setting in these cases and three cats received no chemotherapy.

Pancreatic adenocarcinoma is an aggressive disease in humans with reported 5-year survival rates of only 5%. Human patients are diagnosed with advanced disease at the time of presentation in 80–85% of cases, which further reduces the 5-year survival rate to 2%.[7] The use of gemcitabine has been considered the standard of care in terms of chemotherapy since the 1990s. However, given that the survival rate has remained poor, other gemcitabine-based chemotherapy protocols have been investigated, including the addition of oxaliplatin, capecitabine, cisplatin, epirubicin and 5-fluorouracil (5-FU), among others. FOLFIRINOX (folinic acid, 5-FU, irinotecan and oxaliplatin) has also been shown to improve survival over gemcitabine alone.[8]

The use of maximum tolerated dose chemotherapy has been reported in cats with pancreatic carcinoma. Drugs such as gemcitabine, carboplatin, mitoxantrone and combinations of these have all been reported as first-line chemotherapy, with little long-term success.[4,6]

Molecular therapies such as those targeting angiogenesis (tyrosine kinase inhibitors [TKIs]) have been investigated in pancreatic carcinoma in humans. Sunitinib (SU11248 [Sutent; Pfizer]), for example, is a TKI that has been demonstrated to have efficacy in advanced pancreatic neuroendocrine tumours.[9] Vascular endothelial growth factor (VEGF) is involved in tumour angiogenesis in pancreatic carcinoma and its expression has been

shown to be associated with a worse prognosis.[10,11] Platelet-derived growth factor receptor (PDGFR) over-expression stimulates neoplastic conversion of PDGFR-positive cells, and PDGFR signalling can stimulate angiogenesis and recruit pericytes to stabilise tumour vasculature.[12,13] Intratumoral PDGFR signalling has been shown to increase stromal interstitial fluid pressure, which inhibits transport of chemotherapeutics into tumours.[14] PDGFR has been shown to be overexpressed in human pancreatic tumours.[15]

Toceranib phosphate is a TKI with activity against KIT, platelet-derived growth factor alpha and beta, and VEGF receptor 2. In fact, it has a very similar kinome to sunitinib. It has been shown to have efficacy against a range of carcinomas in dogs and to be tolerated in cats.[16,17] A response rate of feline pancreatic carcinoma to toceranib phosphate is currently unknown. The use of TKIs in this disease has been reported, including one cat that lived 792 days with gross disease.[4,18]

To our knowledge, the cat in our report has the longest progression-free interval and survival time post-surgical resection of pancreatic carcinoma treated with toceranib.

Overall, the use of toceranib in this patient over the long term has been very well tolerated. During the course of treatment, the cat developed generalised hypopigmentation of the haircoat. Skin depigmentation has been reported in a dog undergoing treatment with toceranib phosphate, but, to date, this has not been reported in cats.[19] Cutaneous adverse events are commonly reported in people treated with TKIs, including skin and hair depigmentation. Side effects such as xerosis, paronychia and skin rashes that carry significant morbidity in some human patients were not observed in this case.

Conclusions

Early detection and treatment likely improve the outcome for cats with pancreatic adenocarcinoma. The usefulness of toceranib phosphate in this disease warrants further investigation.

Ethical approval This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not necessarily required.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken (either prospective or retrospective studies). For any animals or humans individually identifiable within this publication, informed consent (either verbal or written) for their use in the publication was obtained from the people involved.

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