

Feline mast cell tumors, a review

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## **Abstract**

Mast cell tumors (MCTs) account for up to 15% of all tumors in cats, and have been reported as the third most frequent tumor in cats after lymphoid and mammary neoplasms. Feline MCTs can be divided into three forms based on anatomic location: cutaneous, splenic, and intestinal. Although cutaneous MCTs were once thought to be invariably benign, some are capable of disseminating and metastasizing; therefore, it is important to distinguish these tumors, in order for appropriate treatment to occur / be implemented. Splenic and intestinal MCT seem to have worse prognoses, although there is less literature documenting these forms of feline MCT. Several chemotherapeutics have been investigated in the setting of canine MCT, and recently, toceranib (Palladia) has been approved by the FDA as a targeted chemotherapeutic agent for management of canine MCT. However, studies on the effectiveness of conventional chemotherapeutic agents for the treatment of feline MCT are rare let alone studies on specific therapies to manage this disease in cats. This review summarizes the current diagnostic avenues to detect and characterize mast cell disease in felines and the available treatment options and shows the need for further research into this important disease in cats.

## Table of Contents

List of Tables.....	v
List of Acronyms.....	vi
Introduction.....	1
Cutaneous Mast Cell Tumors.....	3
Splenic Mast Cell Tumors.....	7
Intestinal Mast Cell Tumors.....	11
Mast Cell Tumors in Non-domesticated Cats.....	13
Discussion.....	14
References.....	18

## List of Tables

Table 1. Comparison of histotypes of feline cutaneous mast cell tumors.....5

## List of Acronyms

<b>Acronym</b>	<b>Full name</b>
BC	Buffy coat
CMCT	Cutaneous mast cell tumors
FNA	Fine needle aspirate
GI	Gastrointestinal
HpF	high power field
MCT	Mast cell tumor
MI	Mitotic index
MST	Median survival time
RTK	Receptor tyrosine kinase
RTKI	Receptor tyrosine kinase inhibitor
SCF	Stem cell factor
sMCT	intestinal sclerosing mast cell tumor

## Introduction

Although a lot of attention is placed on canine mast cell tumors, there is a high incidence of feline mast cell neoplasms that deserve extensive research. Cutaneous MCTs are the second most common skin tumors in cats in the United States and yet, there is no consensus on a reliable grading system, standard-of-care treatment options, or prognostic indicators of disease outcome [1]. Similarly, splenic MCT is the most common splenic disease in cats, but biologically behaves differently from cutaneous MCT, and standards for treating and monitoring this specific disease are also lacking [2]. Finally, following lymphoma and adenocarcinoma, intestinal MCT is the third most common type of cancer in the gastrointestinal system of cats [3]. Intestinal MCT has historically been reported to have a poor prognosis with rapid metastasis to other organs, and this form of MCT also needs investigation into more efficacious therapeutic approaches. The objective of this paper is to review current diagnostic and staging procedures, as well as treatments and associated outcomes for the spectrum of feline mast cell neoplasms, in order to identify areas for further research.

Mast cells are heterogeneous white blood cells present in many tissues, including the skin, respiratory and gastrointestinal tract, but are rarely seen in normal conditions in systemic circulation. Similar to other leukocytes, mast cells derive from pluripotent hematopoietic stem cells of the bone marrow; then, unlike other leukocytes, these cells leave the bone marrow as precursor cells and differentiate to mature mast cells in connective tissue or mucosa, while retaining the capacity to proliferate [4]. Differentiation, regulation, proliferation and migration of mast cells is driven by stem cell factor (SCF), otherwise known as *c-kit* ligand [4, 5]. The *c-Kit* proto-oncogene encodes a receptor tyrosine kinase (RTK) that is a transmembrane

receptor that consists of five immunoglobulin-like domains (IgD) extracellularly, a transmembrane domain, and an intracellular domain that includes the juxtamembrane and kinase domains [6].

Under normal circumstances, mast cells have a role in allergic and inflammatory reactions, wound healing, immune tolerance, and defense against pathogens. Mast cells possess surface-bound IgE that aggregate in response to specific antigens, thus triggering intracellular granules containing biogenic mediators, such as histamine, heparin, serotonin and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) to mediate these various roles [7, 8]. Mast cells, upon stimulation, can also produce proteases such as chymase and trypase, cytokines, growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), leukotrienes and prostaglandins [9]. However, because mast cells differentiate in physiologically / environmentally diverse tissues, they may contain varying types and amounts of these mediators in their granules, and can behave variably. Mallett *et al.* performed immunohistochemistry on different feline MCTs and found that 28%, 18% and 53% of cutaneous, splenic and gastrointestinal (GI) MCTs showed histamine immunoreactivity, respectively [10]. Unexpectedly, serotonin was only detected in 20% of intestinal MCTs and 3% of cutaneous MCTs [10].

Little is known about the etiology of this disease process as it has not yet been linked to a viral or environmental cause. Mast cell tumors arise from the excessive proliferation of genetically aberrant / abnormal / altered mast cells, and yet the underlying etiology for the genetic alterations, especially in cats, remains unknown. Mutations in *c-Kit* and aberrant cytoplasmic localization of Kit have been associated with increased cellular proliferation and reduced overall survival rates in canines [11]. Recent studies have shown that the mutations



commonly seen in canine MCTs are not the same ones found in feline MCTs [12-14]. Gain-of-function mutations within the *c-kit* proto-oncogene induces constitutive ligand-independent kinase activation in humans and dogs and allows mast cells to proliferate uncontrollably [15]. In cats however, the mutations are internal tandem duplications on exons 8 and 9 which affects the fifth immunoglobulin-like domain and these mutations occur in almost 70% of feline cases [14]. Although the biological function of this domain is unknown, these mutations allow the protein to be phosphorylated independent of ligand binding and is thought to contribute to neoplastic proliferation of mast cells [13]. However, it is unknown why mast cell tumors arise in different locations and why feline mast cell tumors behave so differently from the canine forms of mast cell disease.

### **Cutaneous Mast Cell Tumors**

Cutaneous mast cell tumors (CMCTs) account for up to 21% of all cutaneous neoplasms [1, 16]. Cats of all ages can be affected by CMCTs with a range of 4.5 months to 20 years and mean age of 8-10 years [17, 18]. CMCTs on clinical presentation appear as discrete, nodular or papular lesions in the dermis and/or subcutis, that may or may not be ulcerated, and generally range in size from 0.2 to 3 cm [19-21]. Upon manipulation of the tumor, mast cell degranulation may occur resulting in erythema and wheal formation, otherwise known as Darier's sign; however, this finding is uncommonly reported in cats [22]. The tumors are more generally solitary nodules but 20% of cats have multiple cutaneous tumors [1, 23]. The head and neck are the most commonly affected locations in the cat, but tumors may also appear on the limbs, thorax and abdomen [18, 20].

Feline CMCT can generally be easily diagnosed by cytologic examination of fine needle aspirate (FNA) of the mass(es). Staging of CMCTs should include a thorough physical examination for any other tumors; this should involve evaluation of local lymph nodes as well as abdominal ultrasound for potential splenic involvement.

Feline CMCTs are classified histologically into two groups: mastocytic and atypical. The mastocytic-type is further subcategorized into two additional groups; well-differentiated and pleomorphic [24]. Well-differentiated, mastocytic-type tumors are the most common. These are unencapsulated, dermal masses, composed of sheets of mast cells, with few infiltrating eosinophils, and may or may not have lymphocytic aggregates [21, 25]. The pleomorphic, mastocytic-type tumors are less common. These tend to infiltrate more deeply into the subcutis, are composed of large neoplastic mast cells with eccentric nuclei and prominent nucleoli, and have more eosinophilic infiltration [21, 25]. Atypical MCTs, formerly known as histiocytic-type MCTs, are comparably rare. These are composed of large, polygonal shaped neoplastic mast cells that are poorly granulated and have abundant cytoplasm and large nuclei. These tumors tend to have more eosinophilic and lymphocytic infiltration as well as a higher mitotic index (MI) [21, 25]. Atypical MCTs are more commonly seen in cats younger than four years of age and some studies have shown that Siamese cats tend to develop this type of CMCT more frequently [23, 26]. The characteristics of these three histotypes are summarized in Table 1.

Table 1. Comparison of histotypes of feline cutaneous mast cell tumors.<sup>22,30</sup>

<b>Cutaneous Mast Cell Tumor Histotypes</b>			
	<b>Well-differentiated, mastocytic</b>	<b>Pleomorphic mastocytic</b>	<b>Atypical</b>
<b>Incidence</b>	Most common	Less common	Rare
<b>Location in skin</b>	Dermis	Deeper in dermis and subcutis	Deeper in dermis and subcutis
<b>Description of mast cells</b>	Sheets of relatively normal looking mast cells	Large, neoplastic mast cells with eccentric nuclei and prominent nucleoli	Large, polygonal shaped neoplastic mast cells, poorly granulated, abundant cytoplasm, large nuclei
<b>Infiltrating eosinophils</b>	Few	Moderate	Many
<b>Lymphocytic aggregates</b>	+/-	-	+

The well-differentiated, mastocytic and atypical MCTs generally appear to display benign behavior, and most cats will be cured by surgical removal. Some tumors may even spontaneously regress [26, 27]. However, since CMCT has a predilection for the head, surgical resection with wide / adequate margins can sometimes be difficult or impossible. Interestingly, wide margins may not be necessary. Montgomery *et al.* and Molander-McCrary *et al.* performed studies in cats with periocular, mastocytic-type MCTs and showed that rate of recurrence was low even though half or more of the tumors were incompletely excised, and there was no significant difference in survival time between those that were and were not completely excised [28, 29]. Any time surgical resection or excision is performed for MCTs in any location, perioperative H1 and H2 antagonists such as famotidine, omeprazole, and

diphenhydramine are recommended to counter the adverse effects of potential excessive / significant histamine release [30]. Besides surgery, another therapeutic option was discussed in a retrospective study by Turrel *et al.* showing the effectiveness of strontium 90  $\beta$  irradiation for local control of CMCT with minimal adverse effects [19]. On the other hand, the pleomorphic, mastocytic-type tends to have higher proliferative activity, infiltrates more deeply into the dermis and subcutis, and has a less favorable outcome due to higher metastatic ability, which may indicate that adjuvant therapy may be beneficial in these patients [23]. Other options for recurrent or multiple tumors include systemic chemotherapy and is discussed in-depth in the discussion section as it applies to all three forms of feline mast cell disease.

For all forms, staging may be important to evaluate the extent of disease, especially if multiple or recurring tumors are present or if surgical removal may be challenging. Unlike the Patnaik grading system in canines, there is no consensus on a prognostic grading system for feline cutaneous mast cell tumors. Cats with solitary MCTs tend to have a more favorable outcome than those with multiple CMCTs [21, 23]. Mitotic index is the only prognostic factor that is generally agreed upon and 4-5 mitoses/10 hpf or greater is considered a high mitotic rate [27, 31, 32]. Another prognostic factor may be the localization of KIT protein; cytoplasmic labelling was associated with a poorer clinical outcome than membranous KIT labelling [33]. Cellular pleomorphism and presence of lymphocytic infiltrates are not effective prognostic factors in cats [27, 31]. When applied to feline CMCTs, the Patnaik grading scheme also proved ineffective [31]; recently however, a grading system for CMCT was proposed by Sabbatini *et al.* that divided tumors into low grade or high grade tumors [34]. High grade tumors were classified based on the presence of >5 mitotic figures per 10 high-

power fields and at least two of the following three criteria: tumor diameter >1.5 cm, irregular nuclear shape, and nucleolar prominence/chromatin clusters. The majority of tumors in this study were of the well-differentiated, mastocytic-type however, so this may not be a reliable grading system for all CMCT histotypes.

Overall, cutaneous mast cell tumors are the second, fourth and fifth most common cutaneous tumor in cats in the US, UK, and Switzerland, respectively [16, 35, 36]. Although previously viewed as benign tumors, studies now show that the pleomorphic, mastocytic-type of CMCT tends to have a higher rate of malignancy compared to the other two histotypes and a reliable grading system needs to be put in place in order for clinicians to decide whether additional treatment besides surgery may be necessary.

### **Splenic Mast Cell Tumors**

Another form of mast cell disease in cats is that involving the spleen. This is sometimes termed ‘systemic mastocytosis’, and may involve not only the spleen, but also the liver and bone marrow. Splenic mast cell neoplasia is the most common splenic tumor / disease in cats, comprising 15-27% of all splenic diseases. This form of mast cell disease is much more common in cats than in dogs [2, 37]. Mean age of affected cats was reported as 10 years old [38] while other more recent studies stated the median age as 12 and 13 years old [39, 40], but none of the studies showed a breed or sex predilection.

Presenting clinical signs associated with splenic MCT include vomiting, weight loss, anorexia or inappetance, and lethargy [39, 40]. Vomiting is presumably caused by the degranulation and release of histamine from the mast cells which can cause GI ulcers [41].

Upon physical examination, a palpable splenomegaly was noted on physical examination in 42% of cats; the spleen may feel large and meaty and abdominal distention from effusion may be present [39].

On complete blood cell count, about 48% of cats were anemic and 31-100% of cats had mastocytemia [39, 40, 42]. Mastocytemia, or circulating mast cells in the blood, can be a unique diagnostic finding in cats with MCT. Skeldon *et al.* showed the importance of buffy coat (BC) examination by proving that healthy cats and cats with cutaneous MCT only have no evidence of mastocytemia and all cats with splenic MCT had mastocytemia [42]. Likewise, Garrett *et al.* performed a similar study including healthy cats, clinically ill cats without MCT, and cats with MCT and obtained the same results; the clinically ill cats had either neoplasia, endocrinopathies, or noninfectious inflammatory conditions and none of them had mastocytemia [43]. Piviani *et al.* came to a similar conclusion but also found that cats with multiple cutaneous MCTs had mast cells on BC examination; in addition, two cats with lymphoproliferative disease and one cat with disseminated hemangiosarcoma also had mastocytemia [44]. These papers suggest that BC examination could be used for tumor staging and to monitor cats following treatment for splenic MCT; however, it appears that mastocytemia can be seen with other feline neoplasms as well and further diagnostics may be necessary to determine the specific type of cancer. In dogs however, mastocytemia is nonspecific and also occurs in some inflammatory conditions, hypersensitivities, and other pathological processes [45]. Other serum biochemical abnormalities that may be seen with feline splenic MCT can include hyperglycemia, increased liver enzyme activity, azotemia and hypokalemia [39].

Ultrasonographic studies show many different appearances of splenic mast cell disease where size of the spleen itself is extremely variable. Splenic MCTs have been described as small and hypoechoic; enlarged, irregular in contour, and either diffusely hypoechoic or nodular; or normal in size but nodular and with an irregular contour [37]. Other ultrasonographic findings such as hepatic changes or abdominal effusion in conjunction with the splenic changes may be more suggestive of systemic mastocytosis [37]. Kraus *et al.* showed that mast cells were found in 100% of the FNAs performed on the spleens, 85% of cats had hepatic involvement, and 54% of cats had regional lymph node involvement [39]. Similarly, Evans *et al.* found that 52% and 40% of cats had hepatic and regional lymph node involvement, respectively [40]. FNAs can be stained with Wright's, Giemsa or toluidine blue stain to show the deeply basophilic cytoplasmic granules in the mast cells. For complete staging, thoracic and abdominal radiographs may also be performed.

For systemic mastocytosis, splenectomy is the standard therapy. Cats undergoing splenectomy often have long-term disease-free survivals, of up to three years [41]. Mastocytemia often diminishes or resolves post-operatively [40]. After splenectomy, mastocytemia should be monitored via examination of buffy coat smears because an increase in mast cells may indicate disease progression.

Evans *et al.* performed a study comparing the outcomes of splenectomy and/or chemotherapy [40]. Four groups were compared: splenectomy alone, splenectomy with adjuvant chemotherapy, chemotherapy alone and supportive care. Those that received chemotherapy were given steroids alone, alkylating agent alone, tyrosine kinase inhibitor alone, or a combination protocol consisting of vinblastine and/or alkylating agent with a steroid. The cats that had splenectomy had a median survival time of 856 days while the non-

splenectomy group had a significantly lower MST of 342 days. There was no significant difference between the splenectomized groups with and without adjuvant chemotherapy.

Kraus *et al.* also performed a similar retrospective study of cats with systemic mast cell disease that underwent splenectomy and compared different chemotherapy protocols [39]. The overall MST was 390 days and 74% of cats had a positive response to chemotherapy; however, more research needs to be done with sufficient sample sizes to determine if certain chemotherapeutic agents are more consistently effective for this disease. Five cats had no response to the chemotherapy and those protocols included prednisone alone, vinblastine alone, lomustine alone, and prednisone/lomustine. Therefore, this study shows that combination protocols may be more beneficial for cats with mast cell disease. Additionally, metastasis to regional lymph nodes, administration of a blood product, and either concurrent or historical neoplasia were negatively correlated with survival. Interestingly, this study also showed metastasis to the liver improved MST, but the authors suggest this may be due to a small sample size or at the least, liver involvement may not be a negative survival factor in cats.

In summary, splenic MCTs are common in cats, and deserve more attention. Even though cats that undergo splenectomy can survive for several years, it is unknown whether this population may benefit from adjuvant chemotherapy or what the outcome might be with chemotherapy alone.



## **Intestinal Mast Cell Tumors**

Intestinal MCT in cats is sometimes included under the umbrella term “systemic mastocytosis,” however, intestinal MCT is much less common than splenic MCT and seems to possess a far less positive outcome than the aforementioned splenic disease, hence including both the splenic disease and intestinal disease within the same category would be clinically improper.

Median age at time of diagnosis has been reported as 8 and 13 years by two recent studies and there is no evidence of a breed or sex predilection [46, 47]. Site of tumor origin is most commonly the small intestine, followed by the large intestine and rarely the stomach [46, 47]. The clinical signs upon presentation are similar to those for splenic MCT including vomiting, weight loss, inappetance, and diarrhea [47].

Diagnostically, an abdominal mass is usually present on palpation and ultrasound can also be used to visualize diffuse thickening of the lining of the intestine or stomach; noncircumferential, hypoechoic, eccentric wall thickening; a solitary intestinal mass or multifocal intestinal masses [47, 48]. Additionally, cytology and histopathology are commonly used for diagnosis, although variable granulation patterns have been described. Tumors having poorly granulated mast cells may represent less well-differentiated cells that are more likely to metastasize [46]. With intestinal MCTs, metastasis is common and enlarged mesenteric lymph nodes, hepatomegaly, and/or peritoneal effusion may also be present. Staging should include thoracic radiographs and abdominal ultrasound.

A variant of feline intestinal MCT was reported by Colorado State University as feline intestinal sclerosing mast cell tumor (sMCT). This type of tumor was described as having

dense bands of stromal collagen surrounding and dissecting the neoplastic cells [46]. These tumors also had a low mitotic index, high metastatic rate and a guarded prognosis. The authors suggest that the collagen production may be due to the mast cells releasing fibroblast growth factor and transforming growth factor  $\beta$ 1 that activates fibroblasts to produce collagen [46].

Similar to cutaneous and splenic MCT, treatment of choice for intestinal MCT is surgery with wide margins of 5 to 10 centimeters because it has been found that the tumor itself extends microscopically beyond obvious gross disease [38, 49]. Intestinal MCT has the worst prognosis out of the three forms of feline MCT. The median survival time reported by Barrett *et al.* for feline intestinal MCT was 531 days [47]. The cats in this study received either surgery and chemotherapy, chemotherapy alone, corticosteroid alone or surgery and corticosteroid. Although many different chemotherapy drugs were used in this study, lomustine and chlorambucil were the most common, and prednisolone was the most common corticosteroid. There was no significant difference between cats that did and did not undergo surgical excision or between cats that did and did not receive chemotherapy. There was no significant difference on survival of cats that had a second cancer or when comparing the location of the tumor on the small or large intestine [47].

On the other hand, almost all of the cats with the intestinal sclerosing MCT variant died or were euthanized within two months following initial diagnosis [46]. The cats that received a steroid lived a couple weeks longer than those that did not receive a steroid, and one cat that received eight treatments of vinblastine survived for over four years. No other papers have been published on this variant and it is possible that the authors were describing a different neoplasia such as feline gastrointestinal eosinophilic sclerosing fibroplasia [50].

In summary, intestinal MCT has the worst prognosis out of the three anatomical forms of feline MCT, but is also fortunately the least common. For this reason, the extant literature is limited for this disease. The majority of the literature consists of case reports and case series, with a single phase I clinical trial on tumor-bearing cats in general. Additional studies to better elaborate the history, presenting clinical signs, laboratory results, imaging findings, cyto- and histochemical characteristics, and most importantly the best therapeutic options are needed.

### **Mast Cell Tumors in Non-domesticated Cats**

MCTs do not appear to be limited to domestic felines. Interestingly, there is one report of a captive, 16-year-old female, Indian lion that presented with more than 20 hairless, occasionally ulcerated, cutaneous mast cell tumors containing poorly differentiated mast cells and she was unfortunately euthanized because of the disease [51]. Additionally, there was a documented case of intestinal MCT in a 26-year-old female, black jaguar in a zoo in Brazil that was undergoing routine dental treatment and died under anesthesia [52]. Although no clinical signs were observed, necropsy findings revealed that this jaguar also had splenic and liver involvement. Lastly, a 9-month-old cougar was diagnosed with gastric MCT that obstructed the pylorus [53]. A gastrojejunostomy was performed and the cougar was treated with prednisone for 6 months and cimetidine for 4 months and it appeared clinically normal 6 months after surgery. This case is particularly interesting since only 6% of cats have gastric MCT and the paper suggested that the cougar was cured after surgery and chemotherapy.

## Discussion

The literature review has demonstrated that whilst feline mast cell disease is prevalent worldwide, progress has been slow in adequately describing the various forms of the disease, ascertaining species-relevant causal factors, and most importantly identifying innovative and efficacious treatment options and prognostic factors.

Not only has a causal factor yet to be identified, a standardized grading system has not been put into place for feline mast cell disease. Although the Patnaik grading system has been successfully used to grade tumors in dogs [54], the Patnaik system is not applicable to feline CMCTs and there is currently no other system to help categorize these tumors in terms of prognosis. Therefore, there are no gold standard therapies in cats and many chemotherapy protocols are formulated anecdotally. Many feline CMCTs are thought to be benign but it turns out that this is not the case in up to 20% of tumors that can disseminate and metastasize to internal organs [31]. As previously mentioned, the well-differentiated, mastocytic-type may do well with surgical removal and/or strontium 90 irradiation and therefore have a good prognosis [19, 26]. Recently, Sabattini *et al.* devised a grading system that is applicable to this type of CMCT but it would be highly beneficial to apply this grading system to the other types of CMCT as well; this would finally allow for a standardized grading system across all practices and institutions and set a basis for which specific therapies may be used for the different histotypes. In order to establish this grading system, prognostic factors need to be identified.

Furthermore, in the small amount of research that has been done on feline mast cell disease, almost all of the studies are retrospective. Although retrospective studies are useful to determine disease prevalence, more rigorous, controlled, prospective studies need to be

performed in order to gain valuable information on effectiveness of chemotherapy. For example, Rassnick *et al.* performed a prospective study with lomustine to determine the maximally tolerated dose in tumor-bearing cats [55]. This same author performed a subsequent retrospective study on the effects of lomustine on all three forms of feline MCT [56]. Fifty percent of cats had a complete or partial response, although half of these cats only had primary cutaneous MCTs; the cats with secondary cutaneous MCTs had undergone splenectomies previously and showed no response to lomustine therapy. This study suggests that treatment with lomustine may be a good option for cats with primary cutaneous MCT in situations where surgical removal is not possible or where local treatment was not successful. Another study showed that lomustine is safe to use in tumor-bearing cats and rarely causes lomustine-induced hepatopathy like it does in dogs [57].

Another newer option for the management of mast cell disease are the targeted receptor tyrosine kinase inhibitors. It is now known that mutations in the Kit protein, otherwise known as CD117, are common in felines. The conditional approval for masitinib mesylate, an RTKI used for management of MCT in dogs, has unfortunately recently expired in the US but is still available in Europe. It was used in a prospective study to see if healthy cats could tolerate the drug effects without significant adverse effects [58]. From this study, some adverse effects noted were proteinuria and neutropenia. Additionally, masitinib has shown to be effective against both mutated and wild type forms of Kit so even those cats without the mutation may benefit, suggesting that masitinib may have other unknown anti-tumor effects [59]. Similarly, Lachowicz *et al.* determined the toxicities of imatinib mesylate in tumor-bearing cats [60]. Isotani *et al.* identified the *c-kit* mutation in cats and proved that feline MCTs are sensitive to imatinib mesylate, a RTKI used in humans for chronic myeloid

leukemia and acute lymphoblastic leukemia [13]. Another study showed 56% of tumors had a *c-kit* mutation but found that they did not relate to protein expression or correlate with biological behavior [32]. Further research into this drug and other RTKIs need to be performed in cats in order to determine their true benefit alone and in combination with conventional chemotherapeutic drugs. With this more specialized and targeted chemotherapy, there may be less systemic adverse effects and potentially more curative options besides surgery.

Another RTKI, toceranib phosphate, otherwise known as Palladia, was approved in Europe and the United States for the treatment of non-resectable mast cell tumors in dogs. Harper *et. al.* determined its safety and efficacy in MCT-bearing cats that were concurrently receiving prednisolone and showed that three of the seven cats achieved either complete or partial response to toceranib and the major toxic effects were mild neutropenia or GI upset [61]. Another more recent study that included cats with all three forms of MCT showed that 80% of cats clinically benefitted from toceranib administration and the treatment was well tolerated [62].

Moreover, there are no prospective studies evaluating effectiveness of conventional chemotherapeutic drugs such as vinblastine, doxorubicin, and carboplatin alone or in combination with corticosteroids on MCTs in felines. Although vinblastine and vincristine are commonly used alone or in combination with prednisone and lomustine to treat canine MCTs, there are no studies on the effectiveness of the vinca alkaloids or prednisolone alone on feline MCTs. More prospective studies need to be performed to adequately evaluate the benefits of chemotherapeutic drugs on feline mast cell disease; retrospective studies have many variables

that cannot be controlled and often there is critical information on signalment and duration of disease that is unknown that may be detrimental to the study.

Feline mast cell disease may more closely resemble human diseases than canines; human gastrointestinal stromal tumors (GIST), mastocytosis, acute leukemias, and melanomas commonly carry the same Kit mutations on exons 8 and 9 [63]. This is a great advantage for cats because human medicine is generally years ahead of veterinary medicine and there are several RTKIs already developed for human cancers that may be useful in felines.

In conclusion, mast cell disease is an incredibly important process in felines and there is not an appropriate amount of research to combat it. It is important to devise a standard histological grading system to categorize the types of cutaneous mast cell tumors to determine which type(s) are more aggressive and would benefit from additional therapy. Then, there is a great need for controlled, prospective clinical trials to assess whether chemotherapeutic intervention would be beneficial to MCT-bearing cats, under which clinical circumstances, and potentially which agents would be safe, tolerable, and most effective.

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