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Everything You Need to Know about Cancer Management Mini Series

Session Two: Everything You Need To Know About....Canine Mast Cell Tumours

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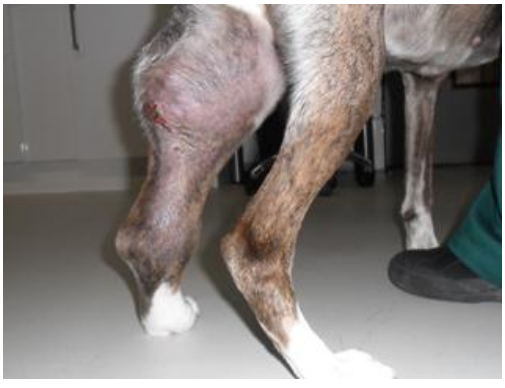

Introduction

Cutaneous mast cell tumours are common in domestic dogs. Many publications cite a prevalence of over 7-21%; these figures are derived from two population-based studies published in 1968 (Dorn and Schneider) and 1974 (Cohen). More contemporary data give an incidence rate, which more accurately reflects the probability of a patient developing a particular complaint, are provided by Dobson et al (2002) who reported a standardised incidence rate of 126 mast cell tumours per 100 000 dogs per year, using data derived from a UK based pet insurance database.

Mast cell tumours are heterogeneous. They are heterogeneous in appearance; they are heterogeneous in clinical behaviour. Canine cutaneous mast cell tumours may exhibit a very benign biological behaviour; they may also exhibit extremely severe biological behaviour. The physical appearance of a mast cell tumour can be a guide but, taken in isolation, does not reliably provide an accurate assessment of tumour severity.

There are numerous treatments reported for the management of canine mast cell tumours. The broad spectrum of biological behaviours seen with this complaint results in confusion in treatment decision-making.

The prevalence, the significant physical and behavioural heterogeneity and the range of appropriate therapeutic options available make mast cell tumours a constant challenge to veterinary practice. It is hoped that this presentation will help to demystify the decision-making process and to improve your management of canine mast cell tumours.

Signalment

There has been no significant age or neuter status association with the development of cutaneous mast cell neoplasia. However, it has been reported by multiple authors that particular breeds are at increased risk of tumour development. Notably predisposed breeds include brachycephalic dogs such as the boxer and Boston terrier, as well as the Labrador retriever, golden retriever and Weimaraner. Boxers, golden retrievers and Weimaraners have also been reported to be at increased risk of the development of multiple cutaneous mast cell tumours; it is wise to forewarn owners following diagnosis of a single mass that others might follow. Mast cell tumours can arise at any age. Peak age incidence occurs at 8 years, but true mast cell neoplasia can be seen in cases only weeks old. Mast cell neoplasia can never be excluded on the basis of age or breed.

Clinical Stage

The differences between outcomes for different patients with the same cancer diagnosis have long been recognised. One source of significant variation in overall survival is the presence or absence of metastasis; this observation led to the development of the TNM clinical stage classification scheme, first published in the context of human breast and laryngeal cancers in 1953. In canine mast cell tumours the presence or absence of lymph node and distant metastases is of enormous prognostic significance. The most common sites of distant metastasis are the spleen and liver.

The prognostic importance of advanced clinical stage cannot be understated, however the frequency with which metastasis develops is relatively low if all mast cell tumours are considered. Extensive investigations to define the presence or absence of metastases are therefore not indicated for all cases with a diagnosis of mast cell tumour. Indeed, overtesting will lead to an unacceptably high incidence of false positive diagnoses. Instead, investigations to define the clinical stage of cutaneous mast cell tumours should be reserved for cases with a real risk of metastasis development.

Histological Grade

In 1973 Bostock published details of a histological grading scheme which separated canine cutaneous mast cell tumours into three distinct prognostic groups. Further refinements and data for a considerably longer period of follow up were presented in a publication by Patnaik et al in 1984 which similarly defined three distinct prognostic groups, using slightly different criteria and it is this scheme that is largely followed today. A revised grading scheme was proposed by Matti Kiupel and colleagues in a publication in January 2013 and it is surprising how widely this grading scheme is also cited in everyday histology reports.

The essence of the Kiupel scheme is that cases are divided into two groups, low and high-grade. This scheme does not benefit from the decades of use and validation of the Patnaik scheme and in my opinion does not represent a forward step.

The observation that definition of histological grade can provide the capacity to predict biological behaviour of the tumour, including risk of metastasis, is of enormous importance to rational mast cell tumour management.

According to the work of Murphy et al, the incidence of metastasis among patients diagnosed with a grade 1 mast cell tumour was 0%. Grade 1 mast cell tumours consistently represent approximately 13-26% of all reported cases diagnosed in first opinion practice. If histological grade were an utterly reliable predictor of biological behaviour, there would be no value in any clinical stage evaluations in any grade 1 mast cell tumour case. However, work by Nicole Northrup (published in 2005) should prompt a degree of caution. In these two studies ten specialist pathologists were invited to provide a histological grade for the same 60 mast cell tumour specimens. Initially there was only 50.3% agreement between pathologists. This rose to 62.1% when all pathologists were given precisely the same histological grade criteria by which to evaluate the tumour specimens. Still over one third of cases were not assigned the same histological grade by all pathologists.

While histological grade is a very useful predictor of biological behaviour in canine cutaneous mast cell tumours, it should always be remembered that the role of histological grade is to aid the clinician by acting as a proxy marker of future biological behaviour. If the tumour already exhibits clinically severe biological behaviour, the histological grade has limited purpose, as future behaviour can already be adequately determined.

Biological Behaviour

Most canine cutaneous mast cell tumours are presented simply as a focal cutaneous or subcutaneous mass. Much is written about the risk of mast cell degranulation and the local or systemic effects of the release histamine and other vasoactive substances, but these effects are rarely noted.

Local effects include: tumour enlargement, induration, reddening and development of peritumoral oedema in response to handling or manipulation; waxing and waning tumour size; marked erythema of the tumour, and persistent dripping blood after fine needle aspirate. Systemic effects include: urticaria; syncope; gastritis/gastric ulceration; DIC; anaphylaxis, and death. Degranulation associated effects are typically triggered by mast cell tumour handling, if they happen at all, though some effects, including spontaneous changes in tumour size, can be seen without any apparent trigger. Patients with advanced metastatic mast cell neoplasia characteristically exhibit a markedly elevated plasma histamine concentration and are more likely to exhibit gastrointestinal and haematological consequences of mast cell activation or degranulation.

Low grade mast cell tumours will typically present as a long-standing cutaneous lesion that is neither painful nor reactive to manipulation. These lesions are expected to be relatively small. By contrast, you would be well advised to adopt a more open-minded approach regarding the potential behaviour of any mast cell tumour, even those diagnosed as grade I, that measures more than 2cm in diameter.

Intermediate grade mast cell tumours comprise 50-80% of all mast cell tumours. This group contains some tumours that exhibit virtually benign behaviour, others that are aggressive and metastatic and a spectrum of behaviours in between. The range of possible behaviours seen with intermediate grade mast cell tumours makes it harder to provide useful generic advice, see below.

Poorly differentiated, or high-grade mast cell tumours are characteristically aggressive in their behaviour and frequently undergo metastasis.

Diagnosis

Mast cells have very characteristic microscopic appearance. This renders diagnosis of cutaneous mast cell neoplasia straightforward in most cases by simple application of a fine needle aspirate biopsy. All practitioners with a clean microscope and appropriate cytological stains should feel confident to diagnose the presence of mast cells in a cutaneous mass by in-house cytology. Developing the confidence to make this diagnosis can dramatically enhance the service offered to your clients by providing a clear diagnosis in a speedy and cost effective fashion, typically without requiring sedation or anaesthesia.

Cytological evaluation does not, however, provide detail regarding the histological grade of the tumour as this is defined partly by cellular criteria and partly by architectural detail. Some cytopathologists will comment that a cytological specimen has features consistent with a tumour of a particular grade but it must be emphasised that the purpose of this comment is to assist the clinician in decision making rather than to provide a definitive tumour grade.

Biopsy techniques available include incisional biopsy, for example using a skin (Keyes) punch or an incisional wedge biopsy technique, or excisional biopsy. Definition of histological grade requires evaluation of the interface between the tumour and the normal cutaneous tissue so the biopsy must incorporate the tumour border for a complete evaluation to be performed. Some thought should therefore also enter into biopsy planning to ensure that the resulting biopsy tract can be easily incorporated into a subsequent definitive excision.

The advantage of incisional biopsy is that it permits appropriate treatment planning without risking compromising the definitive surgical removal of the tumour. The disadvantage that is perceived by many practitioners and clients alike is the need for two anaesthetic procedures, assuming that surgical removal is considered appropriate following biopsy. This supposed disadvantage needs to be measured against the catastrophic disadvantage of incomplete removal of a mast cell tumour due to speculative surgical planning and subsequent loss of the ability to cure what was previously a curable tumour. The former patient will have one extra visit to the veterinary hospital; the latter patient will die of cancer.

The indications for excisional biopsy are the biologically low grade tumour and tumours in an anatomic location where surgical margins are defined by local anatomy rather than tumour grade, for example the digit. Biologically low grade tumours would be defined by indolent behaviour, small tumour size, absence of ulceration or reactivity in response to manipulation and cytological evidence of cellular characteristics that would be consistent with a low histological grade tumour.

As noted above, it is an established fact that there is a risk of inducing histamine release and local or systemic consequences by manipulation of cutaneous mast cell tumours. Various strategies are reported to diminish this risk. The first point to make in this context is, however, that these events do not arise without due warning. Tumours that will induce severe systemic consequences in response to sharp incision and gentle surgical handling are also likely to induce urticaria at the very least, on initial physical examination and fine needle aspirate biopsy. Tumours that might induce significant local signs in response to biopsy will typically show a mild local erythema and oedema in response to handling and will be expected to exhibit prolonged dripping blood loss after fine needle aspirate biopsy.

The agents that are most frequently used to diminish the risk of local or systemic consequences of mast cell activation or degranulation are dexamethasone and chlorphenamine. My cases all receive intravenous chlorphenamine at induction of anaesthesia. Dexamethasone is reserved for cases that demonstrate marked tumour enlargement, urticaria or hypotension during pre-surgical tumour-handling. Systemic manifestations of mast cell activation are typically seen with advanced metastatic disease in which case surgery is contraindicated. Local signs indicate a tumour of intermediate to high grade and treatment plans are made accordingly.

Prognosis

As noted above, prognosis is closely linked to tumour grade and to the clinical stage of the tumour. Prognosis does not only describe the probability of death or survival; it is more appropriate in some instances to regard prognosis as a measure of the probability of tumour recurrence or of quality of life altering complications during diagnosis or therapy.

Most grade I mast cell tumours have zero or only limited capacity for local infiltration and no capacity for metastasis. Very rare instances of grade I mast cell tumours that do exhibit aggressive behaviour are reported, but typically the wary clinician will have noted that the clinical behaviour of these tumours is consistent with aggressive mast cell neoplasia prior to obtaining an incisional biopsy to define tumour grade. Therefore, the clinical behaviour of the mass is inconsistent with the histological grade and under these circumstances, the aggressive clinical behaviour should be considered more representative of the ultimate behaviour of the tumour than the histological grade.

It is often stated that approximately 15% of intermediate grade mast cell tumours exhibit metastasis. Some of these cases can be identified before definitive therapy is undertaken, for instance by recognition of an enlarged regional lymph node with metastasis confirmed by subsequent fine needle aspirate biopsy. Further refinement of the intermediate grade designation is desirable, see below.

High grade tumours metastasise in 80-95% of cases. In the absence of medical therapy, most high-grade mast cell tumours cause the death of the patient within six months of diagnosis.

Further Diagnostic Tests

Frequently, routine diagnostic evaluations prove inadequate, largely due to the relative frequency of intermediate grade tumour diagnoses. A number of ancillary evaluations have been reported which are worthy of discussion.

Mitotic index

A paper by Romansik and colleagues reported the significant prognostic impact of high or low mitotic index in a population of cutaneous mast cell tumours. This was not entirely new, as mitotic index was a feature of previously described histological grading schemes. However, the results were highly significant and this simple test can be performed on every histological mast cell tumour submission without extra work or cost. The median survival time for tumours with a mitotic index greater than 5 was less than 2 months; the median survival time for tumours with a mitotic index less than or equal to five was greater than 70 months. The prognostic significance of mitotic index remained even when allowance was made for histological grade. In the study, most cases with a mitotic index of 5 or less had a mitotic index of one or zero. The ability of this study to predict outcome for cases with a mitotic index between two and five should be questioned due to low case numbers in this range. The fact remains; mitotic index is a powerful predictor of outcome.

Ki-67

Two papers by Tim Scase and others highlighted the remarkable predictive capacity of Ki-67 immunohistochemical staining characteristics in intermediate grade mast cell tumours. In the second study by this group, a previous observation was validated: 95% of dogs with an intermediate grade mast cell tumour exhibiting a Ki-67 index of less than 1.8% were alive 3 years after diagnosis. By comparison, the 1 year, 2 year and 3 year survival proportions for dogs with intermediate grade mast cell tumours with Ki-67 indices of greater than 1.8% were 54%, 45% and 33%, respectively.

The second study validated the conclusions of the first study beautifully, however, other workers do not consistently achieve comparable results and this highlights a difficulty with reliance on semi-quantitative assays. In immunohistochemistry evaluations, specimens are processed to permit antigen retrieval from a formalin-fixed specimen. Variations in the antigen retrieval process will result in variation in the result achieved. Other users prefer to use the combination of Ki-67 and AgNOR markers, which has also been shown to discriminate between mast cell tumours with and without a significant risk of recurrence or metastasis.

c-kit immunohistochemistry and DNA sequence analysis

There are a number of reports from the group of Webster and Kiupel in particular describing the variation in c-kit immunohistochemistry among mast cell tumours and reporting prognostic implications of different immunohistochemical staining patterns. There is some confusion that prevails however, about the utility of c-kit immunohistochemistry in the identification of mast cell tumours that will, or will not, exhibit sensitivity to c-kit inhibitors such as masitinib and toceranib. Tyrosine kinase inhibitors exert their effects through inhibition of an altered c-kit molecule and to definitively recognise this, cDNA or DNA sequence analysis must be performed. This can be a considerably more prolonged procedure taking up to a month. This delay does have obvious adverse implications for therapy.

Treatment Options

There are multiple treatment options available for the management of canine cutaneous mast cell tumours. The vast heterogeneity in mast cell tumour behaviour indicates that treatment selection must be individualised to the patient and tumour in each case.

Treatment options include surgery, chemotherapy, radiotherapy, corticosteroids and tyrosine kinase inhibitor therapy. These treatments are frequently combined in appropriate circumstances.

Surgery

For low grade tumours surgery is appropriate in all cases except where anatomic constraints dictate otherwise. In a study by Amelia Simpson et al, grade 1 and grade 2 mast cell tumours were excised with a 3cm margin of apparently normal tissue and one clean deep fascial plane, according to the prevailing wisdom of the time.

The excised tissue specimens were then cut at 1cm, 2cm and 3cm from the gross tumour margin and all specimens were examined for the completeness of tumour removal at each of the measured margins. All grade 1 tumours were apparently cured by excision with a 1cm margin.

It is reasonable to extrapolate from this study that most other grade 1 mast cell tumours would be cured by similar surgery (1cm margin) provided that the surgery was performed appropriately and that the tumour exhibited biological characteristics consistent with a truly low grade lesion. Thus tumours less than 1cm in diameter with a chronic history are favourable candidates. By contrast, tumours that exhibit variable size, ulceration, reactivity on manipulation, that are greater than 1cm in diameter, are painful, indurated or erythematous are not good candidates for such conservative management and the histological grade in these cases should be questioned.

Intermediate grade tumours have the capacity to undergo significant infiltrative growth and to undergo metastasis. For this reason the clinician should be cautious in the approach to these tumours. Mast cell tumours that undergo metastasis do so preferentially to the regional lymph node. Therefore, the regional lymph node must be evaluated in the preliminary assessment of these cases. All enlarged lymph nodes should undergo fine needle aspirate biopsy. Identification of isolated individual mast cells is of no consequence but the presence of small clusters of mast cells or the identification of mast cells exhibiting cellular atypia indicates regional lymph node metastasis, in which case consideration must be given to systemic therapy; further clinical stage determination exercises are indicated for prognostic and therapeutic decision making purposes.

Some practitioners advocate lymphadenectomy in cases with diagnosed regional lymph node metastasis but an absence of evidence of systemic spread. This is rarely a constructive exercise. It is sadly naive to imagine that the metastatic mast cell tumour is arrested in its progression on encountering the regional lymph node, regardless of the quality of the clinical stage determination investigations. Lymph node removal can be part of the diagnostic evaluation however for cases suspected of having the capacity for metastasis for which medical decisions are yet to be made. Lymph node removal has been shown to have a positive impact when it is used as part of a much more comprehensive multi-modality treatment strategy incorporating radiotherapy and chemotherapy as well.

There is a body of largely anecdotal data reporting increased propensity for infiltrative growth, local recurrence and metastasis in cutaneous mast cell tumours arising in the scrotal or perineal, inguinal and parapreputial regions. Many oncologists always view intermediate grade tumours arising in these locations as potentially metastatic and are more likely to undertake detailed clinical stage evaluations prior to formation of a definitive treatment plan than for intermediate grade mast cell tumours arising in other body locations.

Most intermediate grade mast cell tumours are, however, relatively innocuous in their biological behaviour. In the study by Simpson et al referred to above, 75% of grade 2 mast cell tumours would have been successfully resected employing only a 1cm surgical margin and 100% would have been successfully removed by a 2cm lateral margin. The challenge in managing intermediate grade mast cell tumours is in correctly identifying those which require a greater level of caution and further investigation and those that do not.

High-grade mast cell tumours are rapidly progressive, significantly infiltrative and frequently metastatic. In general, surgery is contraindicated in high grade mast cell tumours, as it is likely to result in failure to achieve the desired outcome, complete removal of the primary tumour, and it carries a significant risk of inducing unwanted and potentially troublesome complications. Systemic therapy is indicated in most cases. Detailed clinical stage determination evaluations should be performed prior to embarking upon definitive therapy to define prognosis and for therapeutic decision making.

Following surgical removal of a cutaneous mast cell tumour it is important that the excised specimen is submitted for histopathological evaluation. The purposes of this are to confirm the diagnosis and tumour grade, histological evaluation of an incisional biopsy can underestimate the grade of a tumour, and to define the completeness of removal. It is interesting to note that a number of studies have relatively recently recognised that the histological reporting of incomplete or marginal removal of cutaneous mast cell tumours is not necessarily predictive of tumour recurrence. Recurrence rates range from 10-28% for incompletely resected canine cutaneous mast cell tumours, an important consideration when contemplating adjuvant therapy. This relatively recent finding is also of enormous importance in the evaluation of historical data reporting the apparent success of adjuvant chemotherapy or radiotherapy in the management of apparently incompletely resected cutaneous mast cell tumours.

Chemotherapy

There are multiple chemotherapy protocols reported for the management of canine cutaneous mast cell tumours. Most protocols incorporate one or both of vinblastine and lomustine.

Vinblastine is a vinca alkaloid that acts by interference with tubulin polymerisation and therefore with formation of the mitotic spindle in cells undergoing mitosis. The principal toxicity with vinblastine is myelosuppression; other less frequently reported toxicities include gastrointestinal signs and peripheral neuropathy. Vinblastine is administered by intravenous injection via an intravenous cannula. Extravasation will result in moderately severe soft tissue necrosis and sloughing.

The dose of vinblastine in common use is $2mg/m^2$ once every one to two weeks. Blood should be obtained for haematological evaluation prior to the second treatment and subsequently as indicated by the results of that evaluation and standard approaches to chemotherapy management. Vinblastine is typically administered in conjunction with prednisolone at reducing doses over a twelve week period. Side effects of vinblastine are relatively predictable.

Lomustine is a nitrosourea alkylating agent. Cytotoxicity is not cell cycle dependent. The beneficial effects of lomustine can be slow to manifest in some cases. Toxicities associated with lomustine are significant. The primary toxicities are myelosuppression and gastrointestinal signs, both of which can happen within as little as four days of treatment administration. Additional side effects include fatal cumulative hepatotoxicity (incidence 17% in one study), fatal cumulative thrombocytopenia, fatal cumulative nephrotoxicity, and interstitial lung fibrosis.

Lomustine is less predictable in its induction of adverse effects than vinblastine so the clinician must be vigilant at all times. Serial monitoring by means of blood testing to evaluate haematological, hepatic and renal parameters should be considered mandatory prior to every treatment administration. Lomustine is administered orally and this can fool the unwary into feeling that it is a less hazardous product; this could not be more wrong.

The dose of lomustine used in the management of cutaneous mast cell tumours is 70-90mg/m^2 once every 3-6 weeks. The interdose interval is defined by the duration of myelosuppression and by the perceived risk of cumulative toxic effects.

A relatively recent study by Maureen Cooper and colleagues reported the use of vinblastine in combination with lomustine for the management of intermediate to high-grade cutaneous mast cell tumours. Results were favourable compared to previous reports using either agent in isolation. Toxicity was not considered severe. The lomustine dose used varied but the average dose was approximately 60mg/m^2. This work requires validation by other oncologists before becoming widely accepted.

A further recent noteworthy publication reported on the use of chlorambucil and prednisolone for the management of unresectable mast cell tumours. A 38% response rate was reported with a median remission duration of 533 days. The results compare favourably with expectation but may reflect rarefied case selection. This option should be of interest to readers who encounter patients for whom risks of toxicity are a major concern. Again, validation by other oncologists is necessary before this treatment plan becomes widely accepted.

Radiotherapy

Radiation therapy is used in two contexts in mast cell tumour management. One is for adjuvant therapy of apparently incompletely excised primary tumours or regional lymph nodes; the second is in the management of gross tumours that are considered unresectable.

Radiotherapy for apparently incompletely resected mast cell tumours can be considered to be highly effective. However, it is impossible to measure the true efficacy of the therapy. We are increasingly aware that a significant proportion of the cases reported that received radiotherapy following apparently incomplete surgical resection are likely to have been cured prior to radiotherapy, as alluded to previously. Some cases receiving radiotherapy in the context of measurable macroscopic disease are regarded a treatment success because their tumour did not progress as quickly as was anticipated; this logic is flawed because it is also known that some mast cell tumours can remain static for months or even years in the absence of therapy. There is no doubt that adjuvant radiotherapy does have a role in mast cell tumour management, but it is also true that this therapy is not without risk. Therefore, cases should be selected on the basis of an informed risk/benefit analysis. Risks associated with radiotherapy include acute severe moist desquamative dermatitis, chronic ulcer formation, pathological fracture, tendon rupture and radiation induced neoplasia.

There is more substantive and measurable evidence for the efficacy of radiotherapy in the management of gross macroscopic unresectable tumour. In the study which best illustrates this, 88.5% of patients demonstrated a complete or partial remission in response to treatment. The median progression free interval was 1031 days. Most of the cases treated were intermediate grade tumours that were considered non-resectable; only 1/29 tumours with a histological grade was grade 3.

Tyrosine Kinase Inhibitors

This is an exciting time in veterinary medicine. We are fortunate enough to bear witness to the arrival of the designer medicine era. To date, medicine has been a science of empiricism, with elaborate therapies defined by experience of learned individuals. We are now in a new era: medicines can be designed according to an understanding of the molecular biology of a specific lesion. In this case, some cutaneous mast cell tumours have been shown to demonstrate mutation of a cell surface growth factor receptor called c-kit. This molecule, under normal circumstances, transduces extracellular growth signals into nuclear messages to induce growth and mitosis. In some mast cell tumours, this signal is permanently switched

on, resulting in autonomous activation of growth pathways, without the need for an extracellular ligand to trigger the process. Cancer follows.

There are two tyrosine kinase inhibitors licensed for veterinary use in Europe, masitinib (Masivet, AB Science) and toceranib (Palladia, Zoetis). Masivet became available in June 2009 and so oncologists in Europe have greater experience with this agent than with Palladia. The limited published work available for these products provides detail that is hard to apply to the clinical cases that are treated on a daily basis. Safety data are available for both and must be scrutinised by anybody with an interest in prescribing these agents. The most significant differences between the products from a medical perspective are the breadth of activity and the risk of on- and off-target toxicity. Masitinib is a highly focussed targeted therapy, with very few off-target molecular interactions. This results in a very tolerable safety profile. Toceranib has a much broader profile of activity. This will be an advantage in some contexts and not in others. In the context of mast cell tumour management, this results in a significant risk of inducing mast cell tumour cell necrosis and therefore degranulation with an accompanying risk of systemic consequences. Outwith the mast cell tumour arena, the off-target interactions may lead to some very positive anti-neoplastic effects; this has yet to be properly investigated but there have been interesting early reports of other veterinary cancer indications.

Side Effects

It is an important point to make that a new understanding of side effects is required as these agents work in a new way. One of the side effects of masitinib use, the so-called 'protein-losing syndrome' is a completely new phenomenon that will undoubtedly take time and coordinated investigation to thoroughly explore and get to grips with.

Masivet

12.5% of cases receiving masitinib exhibited grade 3 or 4 side effects; these were 5% gastrointestinal, 5% protein-loss and/or renal and 2.5% haemolytic anaemia. Grade 3 can be loosely described as severe; grade 4 as life threatening. The mechanism of gastrointestinal signs is through interference with the c-kit receptor in the intestinal pacemaker cells, the Intestinal cells of Cajal. A high proportion of cases exhibited low grade vomiting or diarrhoea but 94% of these spontaneously recovered without requiring treatment interruption or specific therapy. 7.5% developed protein-losing syndrome; in the first days of masitinib use we would evaluate serum biochemistry and urine protein every three weeks. It is now clear that the mechanism of the protein-losing syndrome is an effect on capillary fenestration diameter permitting egress of slightly larger molecules including albumin resulting in albumin loss from the circulation into the tissue fluid and into the glomerulus. Protein-losing syndrome is entirely reversible. Haemolytic anaemia is unusual. The mechanism remains unknown. The average delay from initiation of therapy to detection of anaemia is 84 days. At the moment the advice must be to withdraw the therapy. Anaemia of chronic inflammatory disease is also seen and should not be confused with life-threatening haemolytic anaemia.

Palladia

34.5% of cases receiving toceranib exhibited grade 3 or 4 side effects; these were mostly gastrointestinal. Experience with the drug has identified other adverse events that were not frequently reported as significant findings in the first clinical trial including spontaneous haemorrhage, marked lethargy and gastrointestinal ulceration. The explanation for the high incidence of severe gastrointestinal side effects is the action of toceranib on blood vessels to the mast cell tumour. Damage to the vascular supply results in necrosis of neoplastic mast cells and degranulation effects. Sudden release of histamine, eotaxin and other inflammatory mediators results in gastric hyperacidity, gastric ulceration, hypotension, renal hypoperfusion, potentially DIC and death.

In the event that toxic effects are noted, treatment should be withdrawn. Exact duration of the period of withdrawal is dependent on the severity of the manifestation of toxicity.

Indications for use

According to the language of the European and American licenses, tyrosine kinase inhibitors are indicated for the management of dogs with recurrent or non-resectable grade II to III mast cell tumours. Since most (~80%) cutaneous mast cell tumours are grade II, these are the tumours most frequently treated and reported.

In a recent long term study reported by Hahn and others (AJVR 2010) only 11/132 mast cell tumours randomized to receive masitinib or placebo were grade III tumours; the remainder were all grade II mast cell tumours. Responses were favourable when masitinib and placebo were compared but responses were far from impressive when the cohort is examined as a whole. Independent clinical casework has revealed a far more impressive response rate when cases are selected on the basis of the presence of clinical indicators of high-grade malignancy. These data are not yet published.

In cats, there are currently no clinical data whatsoever to support the clinical use of toceranib or masitinib; there is simply a single study reporting the pharmacokinetics of masitinib in cats after a single injectable dose. Therefore, there is an absence of safety or efficacy data; everything you read or hear should be regarded as anecdote. Some oncologists will treat systemic mast cell neoplasia in cats on the basis of c-kit mutation status. Cases whose tumours are positive for c-kit are considered candidates for TKI therapy; those without are considered candidates for conventional chemotherapy or corticosteroids.

Conclusions

Canine cutaneous mast cell tumours pose problems for the veterinary clinician through their marked heterogeneity in biological behaviour. Critical elements of the decision making pathway include identification of tumour spread and definition of histological grade. A range of therapeutic strategies is available but no single strategy is applicable in all cases. The development of novel pharmacological therapies holds great promise for the management of canine cutaneous mast cell tumours specifically and for veterinary cancer in general; this will be a fast changing field in the coming years.