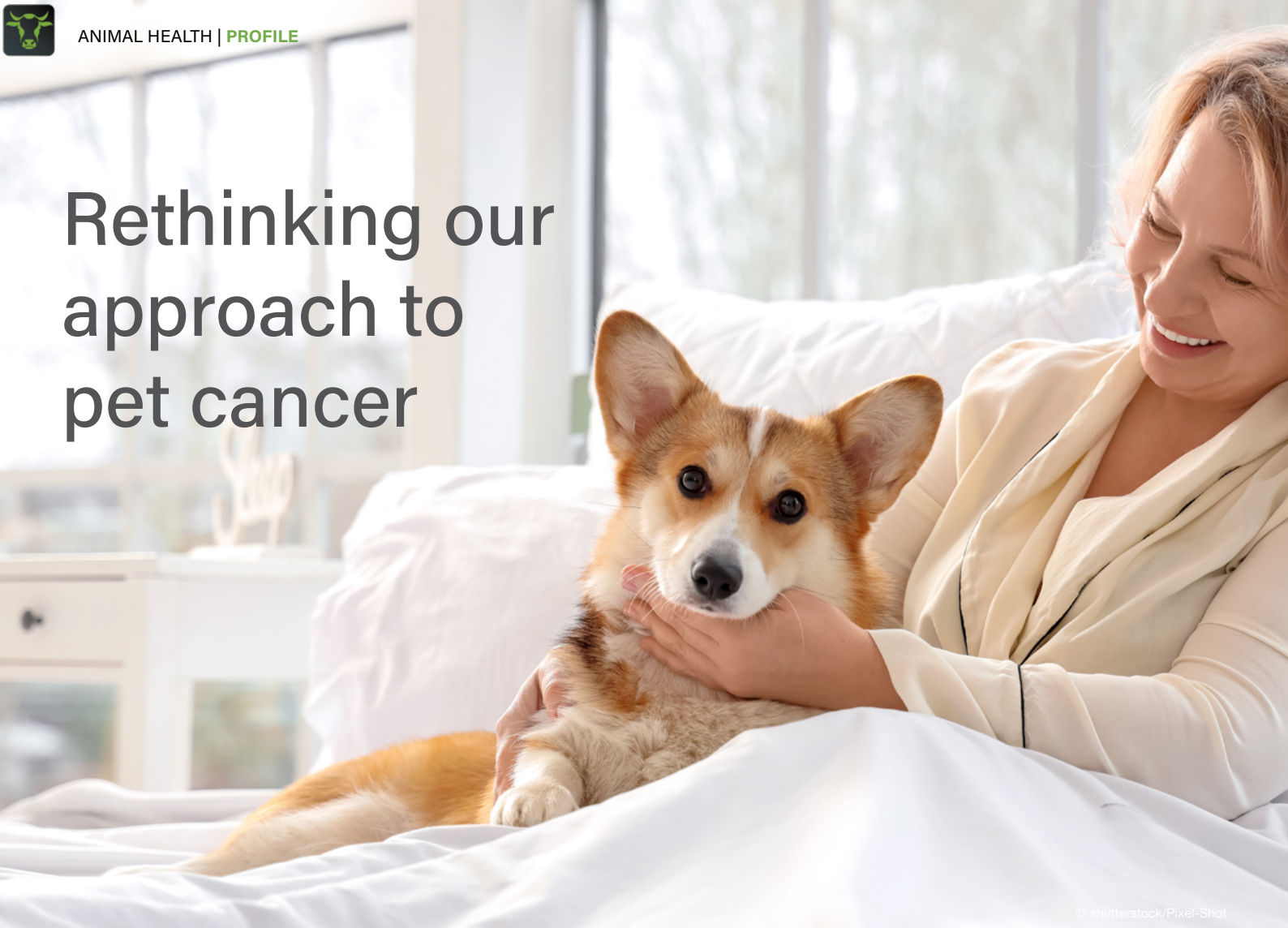




Rethinking our approach to pet cancer



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Kyrexia believes that cancer treatment should be available to all pets at their local veterinary practice, regardless of location, budget, or family circumstance

CANCER is a growing problem, in both pets and humans, and there is an urgency to deliver better treatments and earlier diagnostic tests. There is no doubt that earlier diagnosis offers a better chance of favourable outcome from treatment, especially where tumours can be removed surgically. However, pets still have few medical treatment options for cancer that are both effective to treat the tumour and maintain good quality of life. Will early diagnosis make a real difference to our pets when a cancer that is diagnosed early may not justify a potentially harsh course of treatment?

How are we treating cancer in pets now?

Surgery remains the best chance of cure, but requires removal of not just the tumour but an extra margin of apparently normal tissue which is likely to be infiltrated. As tumours enlarge, their complete removal becomes increasingly difficult without impacting on normal functions. Many tumours are not localised to one site, with spread to local lymph nodes or more distant sites such as lungs, liver or bone. Other forms of cancer (such as lymphoma and myeloma) may affect cells present

throughout the body and these cannot be treated with surgery.

Radiotherapy for pets is generally a local therapy used to shrink tumours or to try to clear surgical sites of residual tumour (dirty margins). It requires specialist facilities, multiple anaesthetics and, in many cases, only offers a delay in tumour growth. It is expensive and can be associated with immediate and delayed side effects which can impact on quality of life.

Medical treatment options present an opportunity to remove tumour cells throughout the body, addressing secondaries in other organs as well as the primary site. Chemotherapy targets rapidly dividing cancer cells at various points in their cycle of growth but this effect also hits normal, rapidly dividing cells such as the bone marrow (where blood cells are made), the lining of the gastrointestinal tract, and hair follicles. These secondary effects are responsible for the side effects we see in humans treated with chemotherapy treatments. Many of us have experience of these



challenges, either directly or through friends or family undergoing cancer treatment, and are understandably fearful of putting our beloved pets through similar treatments.

In order to reduce the risk of chemotherapy side effects in pets, chemotherapy doses are lower than those used in humans. However, the need to destroy the cancer cells means there is a limit to how low the dose can be and the risk of side effects remains. If the treatment killed no cells at all, it would be ineffective. The use of lower doses in our pets means that we are merely providing a palliation of the cancer that buys some time but increases the risk of resistance developing.

There are some licensed targeted therapies available to our pets but, again, these are not as selective as we would hope, and other tissues in the body which express these targets may be damaged. This means they can be associated with similar side effects to chemotherapy treatments.

How did we discover chemotherapy?

Chemotherapy was first identified less than 100 years ago from the discovery that mustard gas (a chemical weapon) destroyed white blood cells, suggesting it could have a role in the management of lymphoma. Scientists then modified known toxic chemicals to make them useful as treatments for cancer. Some drugs were discovered by accident, such as the platinum derivative cisplatin, whose anticancer activity was discovered when researchers noticed unusual effects of platinum electrodes on bacterial cell division. These accidental discoveries were then followed with research identifying the drivers of cancer and potential target mutations, genes, and mechanisms which provided the means to develop more targeted therapies. Systematic screening of chemical libraries revealed even more molecules with anticancer activity. Recently, ecological observation of how wild animals and birds use plants has inspired the discovery of natural products with anticancer effects. Together, these approaches have shaped a diverse chemotherapy arsenal built from wartime chemicals, natural products, synthetic chemistry, and modern molecular biology.

Pets are generally restricted to the earlier types of cancer drug where development was driven by the need to identify a toxic substance that could destroy cancer cells or induce the cancer cells to destroy themselves without causing the same degree of harm to other tissues. These substances were tested first *in vitro* (cancer cells in a 'test tube'), before moving into experimental cancer models such as mice. Tests in laboratory animals have traditionally helped to identify what doses may be unacceptably harmful to a patient. Dogs have been a valuable part of this development story for the older, traditional human cancer treatments.

Whilst initially there was an assumption that the highest possible dose of a treatment had the best chance of success and that dose intervals should be optimised to allow normal tissues to recover (maximum tolerated dose chemotherapy), it has recently been shown that lower chemotherapy doses given more frequently to pets (metronomic chemotherapy) can also be effective by slowing blood vessel growth in the tumour. Although most cancer treatments are re-purposed human cancer treatments that are not licensed in dogs and cats, many have undergone testing in animals prior to their use in humans.

What drives the development of cancer treatments?

What is clear is that the starting point for traditional cancer treatments has been finding a substance that kills cancer cells in a laboratory, and the question that follows is whether the impact on other cells within the body is sufficiently low enough for a drug to be tolerable. We use drugs that may be effective at killing cancer and generally accept that there is likely to be some harm in the form of side effects. Although the balance between benefit and harm is central to all cancer medicines, human and veterinary, the avoidance of harm is even more important when a pet, with no understanding of the choices to be made, has cancer.

What are the major problems pet parents experience?

Cancer affects one in three dogs and one in five cats and remains a major cause of death for both species. The treatment options are limited and many practice veterinarians do not offer them in house. This means that pet parents may have to consider referral with the associated travel and additional costs. There is an enormous, emotionally charged burden placed on people who are managing a pet with cancer, large veterinary bills, and the associated logistical challenges.

Chemotherapy carries a risk of significant side effects which affect quality of life, requires regular blood tests and monitoring, and often needs to be given into a vein. A recent study suggested that **58% of pet owners in the UK would decline chemotherapy due to a fear of the possible side effects**. Some pets will not tolerate the necessary regular hospital visits and the associated travel which can have a deleterious effect on their quality of life.

Toxic chemotherapy by-products are excreted in faeces, urine, and saliva of treated pets, which poses a risk to human health. Family members who are immunosuppressed, pregnant, or breastfeeding should not handle treated pets for a period of time (three to eight days) after each treatment is administered. Young children may also be at risk when playing or petting the dog from saliva contamination or exposure to body fluids. This worries many people, who think: "I want to be able to do the best for my pet, but I want to be able to love them at the same time."



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What are the major problems vets experience when treating pets for cancer?

Improved diagnostic facilities mean that cancer is much easier to diagnose in veterinary practice. Early diagnostic tests are available which provide the opportunity to make a diagnosis prior to symptoms from simple blood tests. However, there are few licensed treatments available and we do not yet know if earlier medical treatment will translate into longer survivals for many types of cancer.

The health and safety implications of administering chemotherapy in a local practice means that many GP veterinarians are unwilling to deliver chemotherapy. There are risks to the staff from the drugs themselves and the patient's body fluids. Some vets also feel that they lack the skills to make complex decisions regarding doses and managing side effects. Many GP veterinarians therefore prefer to refer cancer patients to specialist oncologists for treatment. Whether this is possible will depend on the proximity to a specialist oncologist and the financial position of the pet parents.

For those veterinarians who can administer all types of cancer treatment to pets, there remains the problem of resistance to treatment developing over time. With each exposure to a particular drug, the cancer cells evolve and some cells will find ways to survive. Over time, the cells that remain are resistant to the treatment. Some drugs will also induce multi-drug resistance, which means that the cells can become resistant to a variety of chemotherapy drugs despite not having been exposed to them. Repeated use of chemotherapy drugs that damage the bone marrow can have lasting and irreversible effects on the body's ability to make new blood cells, so, even in pets where there are no financial restrictions, there is a limit to how many times a patient can be treated.

What can we do to change this?

Cancer treatment needs to change for pets in particular. With diagnostic tests advancing rapidly and providing earlier diagnosis, it is essential that we find alternatives to the current drugs, many of which have significant impacts on quality of life. In pets, end of life decisions, including euthanasia, are guided by overall quality of life and therefore survival times are directly influenced by the pet's ability to enjoy life. Earlier diagnosis and earlier exposure to drugs may not lead to longer survival if a treatment spoils the pet's quality of life.

We need cancer medicines for pets that have high selectivity for cancer cells with much less impact on normal cells so we can avoid harmful side effects. High selectivity may come about if the medicine works on the tumour through a variety of mechanisms, which also reduces the chances of developing resistance. For drugs with minimal impact on the bone marrow and intestinal tract, it also means they can be administered for prolonged periods if required.

Pet parents want to be able to prolong their pet's life for as long as possible whilst maintaining the pet's quality of life, allowing them to live life to the full. Pet parents make decisions guided by their pet's quality of life and not by cure alone, and quality of life determines their decisions regarding referral to specialists, treatment intensity, and end-of-life timing. They want a treatment that is, as much as possible, side-effect free, easy to administer, and that does not require their pet to spend too much time at a veterinary hospital. They want to be able to share their beds, hug their pets, and participate in all the activities they enjoyed before their diagnosis.

Treatments that meet these needs will appeal not just to those pet parents already willing to consider currently available cancer treatments, including chemotherapy, but also those who fear the side effects their pets might experience or the health and safety implications for family members. A drug with these attributes would offer an alternative for all pets, including those in the end stages of cancer seeking palliative care after traditional treatments avenues have been exhausted. As pet parents have the ability to choose the time of their pet's death through euthanasia, any treatment that improves quality of life has the potential to extend life, particularly where cancer progression can be slowed or stabilised.

Kinder cancer care is possible

Kyrexia has identified a novel cancer treatment that means pet parents are not forced to choose between a longer life and a happy life for their pet. We believe that cancer treatment should be available to all pets at their local veterinary practice, and not restricted by location, budget, or family circumstance. Pets can then spend as much as possible of their final days at home and live their remaining life to the fullest. The delivery of a medicine that can have a positive impact on the pet's quality of life whilst also slowing the growth of the cancer is within reach.



KYREXIA

Clare Knottenbelt
CEO & Co-Founder
Kyrexia Ltd
07749 865086

