



ONCOLOGY

Emergency in
oncology

Diagnostics of oncology
patients – liquid biopsy

Heart tumors
– therapy

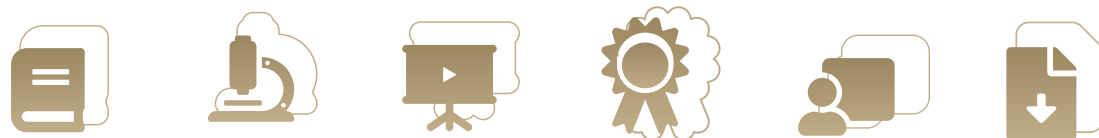


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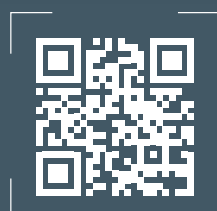
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EDITORIAL PAGE

Dear readers,

We would like to present to you yet another issue of *Veterinary Life* magazine, this time pertaining to Oncology. It is undoubtedly a notably difficult topic, which is frequently perceived by animal owners as the equivalent of death sentence for their pets. Nevertheless, it is not always the case. Various cancer types can be treated. However, it has to be remembered that each tumor type requires an individual approach. Treatment is usually based on combining several therapy-oriented approaches together, namely: oncological surgery, chemotherapy, radiotherapy, and many others. Nevertheless, the early detection of a given disease and a proper diagnosis are of significant importance when it comes to pet's health-related forecasts. Therefore, within the scope of this issue of the magazine, we would like to especially recommend to our readers an article on liquid biopsy, which is an innovative approach to neoplastic disease diagnosis. We would also like to encourage our readers to familiarize themselves with emergency cases related to neoplastic diseases and widely discussed topics of heart tumors and cytostatic medication cardiotoxicity.

We hope you will enjoy this issue!



Agnieszka Kurosad
Editor-in-chief

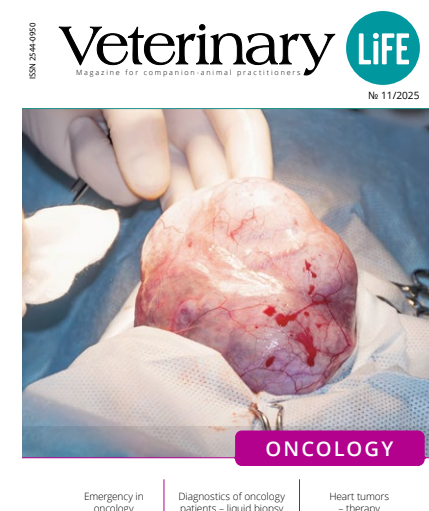


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Emergencies in oncological patients

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Abstract: When it comes to the course of malignant neoplasm, a life-threatening emergency may sometimes occur. Oncological emergencies require rapid recognition and optimal undertakings to be performed. Disorders in such patients are directly or indirectly related to neoplasm, as well as may be the result of their response to oncological treatment. The predominant goal of this paper is to familiarize general practitioners with oncological emergencies in order to improve their both diagnostic and therapeutic skills with regard to managing them.

Keywords: oncology, dog, cat

Introduction

Taking a proper care of oncological patients may pose a remarkable challenge, not only for veterinary oncologists, but for general practitioners as well. An oncological emergency is typically defined as an acute condition directly related to a particular cancer itself, being accompanied by physiological disorders that occur as a result of body-specific changes related to the cancer (paraneoplastic syndrome) or caused by oncological treatment. Such an emergency necessitates swift intervention in order to avoid death or adverse, permanent complications. Within the framework of this review, the pathophysiology, clinical imaging, diagnosis, and treatment of common emergencies in veterinary oncology are going to be discussed in an in-depth manner.

PARANEOPLASTIC SYNDROMES

Malignant hypercalcemia

Hypercalcemia is a common electrolyte disturbance that may be encountered by practitioners specializing in pets. There are several possible causes of hypercalcemia, which can be divided into non-pathological, transient, and pathological ones. Most common causes are pathological ones, which include neoplasms, primary hyperparathyroidism, and acute or chronic renal failure. When it comes to canines, neoplasms are considered to be the most common cause of hypercalcemia. In felines, neoplasms are the third most common cause, preceded only by idiopathic issues and renal diseases (Savary et al. 2000, Scheck et al. 2014, de Brito et al. 2017,

Withrow & MacEwen 2019). In dogs, typical neoplasms associated with the discussed phenomenon include predominantly T-cell lymphomas and apocrine gland anal sac adenocarcinomas (AGASACA) (Bennett et al. 2002, Fournel-Fleury et al. 2002, Williams et al. 2003). Concomitant hypercalcemia is typically associated with a poorer forecast for both T-cell lymphomas and AGASACA (Bennett et al. 2002, Williams et al. 2003). In cats, lymphoma and carcinoma are most common causes of malignant hypercalcemia (Savary et al. 2000, Bolliger et al. 2007). Nevertheless, hypercalcemia may also occur and develop in other types of cancer, including: multiple myeloma, parathyroid tumors, thymus, melanoma, primary lung cancer, as well as acute and chronic lymphocytic leukemia (Withrow & MacEwen 2019). While taking multiple myeloma into account, approximately 20% of patients develop hypercalcemia. In dogs suffering from multiple myeloma, concomitant hypercalcemia is a poor forecasting indicator (Patel et al. 2005). Osteolytic metastases and the resulting excessive release of calcium from bones also cause hypercalcemia. They are most commonly observed in patients with prostate, mammary, liver, and lung cancers (Rosol 2000).

Causes of paraneoplastic hypercalcemia include: the ectopic production of parathyroid hormone (PTH) or PTH-related peptide (PTH-rP), extensive and multifocal lytic bone tumors, tumor-associated prostaglandins (PGE1 and PGE2), 1- β interleukin, transforming growth factor β (TGF- β), and receptor activator of nuclear factor kappa β (RANKL) (Withrow & MacEwen 2019). The excessive production of parathyroid hormone-like protein is one of

most important causes of hypercalcemia in cancer patients. PTH-rP is structurally and functionally related to PTH. It is produced under both normal physiological conditions and by some types of cancer cells (Scheck et al. 2014). PTH-rP stimulates osteoclastic bone resorption, increased renal tubular calcium resorption, as well as decreased renal tubular phosphate reabsorption (Scheck et al. 2014). There are additionally other possible mechanisms connected with either cytokine release or direct release from bone as a result of extensive osteolysis (Kohart et al. 2017). The absence of detectable PTHrP does not exclude hypercalcemia in the course of diagnosed malignancy (Kohart et al. 2017).

Malignant hypercalcemia has a rather broad effect on many organ systems, leading to a variety of clinical symptoms, which may include, inter alia: polydipsia, polyuria, anorexia, inappetence, weakness, and bradycardia (Scheck et al. 2014, Daniels & Sakakeeny 2015, Kohart et al. 2017). When it comes to felines of various breeds, most prevalent clinical signs are anorexia and lethargy, while polyuria/polydipsia and gastrointestinal disturbances are identified remarkably less often (Savary et al. 2000). Hypercalcemia causes both functional and structural changes in the kidneys. It is worth mentioning at this point that the latter may not be reversible, even with the proper treatment regimen being opted for (Scheck et al. 2014). Furthermore, hypercalcemia reduces the excitability of gastrointestinal smooth muscle, while parietal cells may release hydrogen ions in response to HC (Scheck et al. 2014). Clinically significant effects of hypercalcemia on the heart are rare in both dogs and cats. However, arrhythmias may occur due to the effect calcium has on myocardial cells or due to the mineralization of heart tissue (Scheck et al. 2014).

Calcium levels should be normalized in animals with signs of hypercalcemia as swiftly as possible in order to avoid organ damage. It has to be pointed out that long-term management of hypercalcemia requires opting for a definitive treatment of the primary cause. The best approach to limiting effects of malignant hypercalcemia is by means of the effective surgical removal of the tumor or the reduction of tumor volume

by means of conservative therapy (such as chemotherapy for lymphomas and multiple myeloma). If the reduction of tumor volume is not possible, various treatment-specific options may be considered in order to offer help in managing pet's hypercalcemia and secondary symptoms.

PTHrP and iCa concentration levels (and consequently - clinical symptoms) typically tend to improve following the successful treatment of the primary tumor. If critically ill patients are concerned, fluid therapy with 0.9% NaCl promotes volume expansion and diuresis, resulting in both effectively and rapidly diluting calcium levels (Scheck et al. 2014). Loop diuretics may be taken advantage of after hydration. Nevertheless, thiazide diuretics are contraindicated. They should only be used in the case of well-hydrated patients, as well as under a meticulous medical supervision (Daniels & Sakakeeny 2015).

Bisphosphonates (such as zoledronate or pamidronate) induce osteoclast apoptosis, thereby inhibiting calcium release from bone and transiently reducing calcium levels in patients suffering from malignant hypercalcemia (Daniels & Sakakeeny 2015, de Brito Galvão et al. 2017, Schenk et al. 2018). Calcium level reduction typically takes 2–5 days. Effects achieved tend to last for 4–6 weeks (Scheck et al. 2014). The swift intravenous administration of bisphosphonates may increase their nephrotoxic potential. Therefore, their administration at the dose of less than 200 mg/h is strongly recommended by professionals with experience in the field (Adami & Zamberlan 1996).

Once a definitive diagnosis has been made, glucocorticoids may turn out to be useful in reducing calcium absorption and promoting calcium excretion through various physiological mechanisms (Daniels & Sakakeeny 2015). When it comes to patients with steroid-responsive cancers (such as lymphoma and multiple myeloma), glucocorticoids may make future development stage examinations difficult. What is more, if used prior to chemotherapy, they may increase resistance to some chemotherapy-specific agents. In such patients, steroid therapy should be reserved for palliative care or withheld until development stage examination has been performed, followed by a chemotherapy plan implementation.

Hypoglycemia

Insulinoma is the most common neoplastic cause of hypoglycemia in dogs. Paraneoplastic hypoglycemia is also observed, inter alia, in the case of: hepatocellular carcinoma, hepatoma, lymphoma, leiomyosarcoma, adenocarcinoma, and angiosarcoma (Cohen et al. 2003, Liptak et al. 2004, Battaglia et al. 2005). Hypoglycemia in malignant neoplasms is often caused by

the overproduction of insulin or insulin-like growth factors by neoplastic tissue (Finora 2003). During early stages of the disease, patients are clinically stable, as is often seen in insulinoma. Clinical signs, including weakness, ataxia, disorientation, seizures, and collapse, may occur as the underlying disease progresses and hypoglycemia becomes more severe (Goutal et al. 2012).

Before testing for hyperinsulinemia, it is vital to exclude exogenous insulin overdose, adrenal insufficiency, hepatic failure, sepsis, as well as xylitol toxicity. While taking insulinoma into account, the diagnosis of hypoglycemia can be made basing on the insulin-to-glucose ratio. For paraneoplastic hypoglycemia to be diagnosed, there has to be an abnormally elevated insulin level despite marked hypoglycemia, with insulin-to-glucose ratio of >30 (Goutal et al. 2012). Said test has been proven to be accurate only in patients with glucose concentration of <60 mg/dL at the time of its collection. Nevertheless, it has to be indicated that conditions other than insulinoma may result in altered parameters. When it comes to cases where insulinomas are confirmed, the insulin-to-glucose ratio may still be normal, making diagnosis highly problematic (Fernandez et al. 2009). CT and ultrasound scans may provide support in revealing the primary tumor. However, it should be noted that exploratory laparotomy is often required to detect and identify smaller pancreatic tumors (Goutal et al. 2012). As far as extrapancreatic tumors are concerned, determining the exact cause of hypoglycemia may also prove to be troublesome.

The surgical removal of the tumor is recommended with regard to insulinoma, hepatocellular carcinoma, and leiomyosarcoma. Glucose levels usually normalize after surgery, especially after complete surgical excision and no visible metastases (Goutal et al. 2012). Postoperative hypoglycemia is a negative forecasting indicator, mainly due to the fact that incomplete surgical excision or metastases may be associated with hypoglycemia (Goutal et al. 2012). In the acute state, patients with hypoglycemia are stabilized by means of continuous dextrose infusions. Medications, including glucocorticoids, glucagon, and beta-blockers, can also be taken advantage of in order to promote normoglycemia while further research and definitive treatments are being conducted (Smith et al. 2000; Datte et al. 2016). The issue-specific management method is outlined in Table 1.

NEOPLASTIC HEMORRHAGIC EFFUSIONS

In some cases, animals may develop acute clinical symptoms secondary to hemorrhagic effusion from the tumor. The most common

ones are hydropericardium and ascites associated with the tumor. Hemorrhagic pleural effusion is less commonly diagnosed (Nakamura et al. 2008).

Pericardial effusion

Neoplasms are considered by experts to be the most common cause of pericardial effusion in dogs, with most typical areas of development being the right atrium and base of the heart (Vicari et al. 2001; Ehrhart et al. 2002; Johnson et al. 2004). The most common neoplasm responsible for the discussed condition is haemangiosarcoma (HSA). Nevertheless, it has to be pointed out that other neoplasms may also occur, such as heart base tumors, mesotheliomas, and lymphomas (MacDonald et al. 2009).

Most common symptoms observed in dogs include muffled heart sounds, tachypnea, weakness, as well as exercise intolerance (Johnson et al. 2004). Many patients suffering from the discussed health condition may have abnormal electrocardiographic findings (Johnson et al. 2004). Pericardial effusion may also lead to cardiac tamponade development, which is fatal if untreated.

When it comes to animals with pericardial effusion, clinical symptoms may range from weakness to collapse in acute cardiac tamponade. Patients with pericardial effusion exhibit weak peripheral pulse, jugular vein distention, positive hepatjugular signs, difficulty breathing, ascites, as well as excessive vomiting (Fahey et al. 2017, Silverstein D. & Hooper K. 2022). One of typical symptoms is also paradoxical pulse (pulsus paradoxus, PP). In patients with tamponade, blood flow velocity decreases, followed by cardiac output, which results in a significant decrease in systolic blood pressure, being above 10 mmHg (up to 10 mmHg is normal). A paradoxical pulse can be detected during the physical examination of patients. In the course of examination of the femoral pulse, such patients have a weak pulse during inspiration and a stronger one during expiration. The combination of normal physiological displacement of the interventricular septum during inspiration and pathological reduction in left ventricular filling by pericardial effusion results in reduced inspiratory stroke volume and lower femoral pulse on palpation. Paradoxical pulse can be identified in dogs most easily when they assume a lateral position (Shaw & Rush 2007). Echocardiography is the primary diagnostic test characterized by the sensitivity of 82–99% when it comes to identifying heart masses (MacDonald et al. 2009). Cardiac hemangiosarcoma is most commonly located in the right atrium and/or right cardiac auricle (MacDonald et al. 2009; Yamamoto et al. 2013) – Fig. 1.

The primary treatment is mainly based on removing the fluid by means of a properly performed pericardiocentesis.

Arrhythmias, particularly ventricular ones, are the most common complication, occurring in about 10% of canines within an hour of the procedure and in 15% within 48 hours (Humm et al. 2009). What is more, 41% of treated pets with said complication diagnosed have been euthanized or died within 48 hours of diagnosis, with cardiac HSA being suspected in most cases. An intravenous line must be inserted and fluids (colloids and crystalloids) have to be slowly and steadily infused in order to prevent hypotension. Oxygen should be administered as well. Premedication is typically advised to eliminate the risk of cardiac puncture in the event of patient movement. It is of exceptional importance to monitor the heart rhythm during the entire procedure (continuous ECG monitoring). Fluid obtained during pericardial puncture should always be sent for cytological examination. Nevertheless, opting for fluid cytology to make a diagnosis can also give mixed results depending on the etiology. In cases where the effusion is characterized by a low haematocrit, it is more likely to have a non-neoplastic cause. In said scenario, clinicians should consider inflammatory and infectious diseases (Cagle et al. 2014).

Unfortunately, in cardiac hemangiosarcomas, pericardial effusion is likely to recur. The median survival time is consistently less than 30 days (Johnson et al. 2004; MacDonald et al. 2009). Even with various therapies being implemented and taken advantage of, survival times remain short (Weisse et al. 2005; Ghaffari et al. 2014; Mullin et al. 2016). Forecasts appear to be more optimistic for other types of cancer, but it is highly dependent on the type of cancer and treatment used.

Ascites

Similarly to pericardial effusion, spontaneous hemorrhagic peritoneal effusion is a common syndrome observed in pets. In dogs and cats with hemorrhagic peritoneal effusion, the most common cause is malignancy, usually being secondary to splenic injury (Pintar et al. 2003). Hemangiosarcoma (Fig. 2) is the most common neoplasm associated with splenic neoplasia in dogs, accounting for 45–51% of malignant splenic neoplasms (Hammond & Pesillo-Crosby 2008). When it comes to felines, causes of spontaneous hemorrhage into the peritoneal cavity are evenly distributed between neoplastic and non-neoplastic ones (Culp et al. 2010).

Symptoms related to peritoneal fluid accumulation may be nonspecific in nature and include: weakness, ataxia, abdominal distension, collapse, and even death (Pintar et al. 2003). If weakness and abdominal distension are present during examination in association with pallor of the mucous membranes, abdominal imaging (preferably ultrasound) should be performed promptly in order to detect free peritoneal fluid

and intra-abdominal lesions, particularly in the spleen area. If the fluid is present, a sample may be obtained by abdominal puncture to determine whether the fluid is bloody in character. Even when the peritoneal effusion is caused by a ruptured tumor, malignant cells are rarely seen while examining the cytological evaluation of the fluid. Diagnostic examinations and analyses should be performed to establish the cause of the effusion, identify any hematologic abnormalities requiring intervention, and spot metastases before surgical intervention for the malignancy. Blood abnormalities that may be observed in cases of peritoneal bleeding include both regenerative and non-regenerative anaemia, neutrophilia, as well as thrombocytopenia (Pintar et al. 2003). Thrombocytopenia occurs in 75–97% of cases of peritoneal bleeding due to hemangiosarcoma (Hammond & Pesillo-Crosby 2008). Biochemical abnormalities are usually nonspecific in nature (Pintar et al. 2003 and Culp et al. 2008). Coagulopathy occurs in most patients and disseminated intravascular coagulation (DIC) may occur in approximately 50% of canines suffering from hemangiosarcoma (Maruyama et al. 2004 and Mischke et al. 2005). When it comes to hemangiosarcomas, the preoperative diagnosis of the tumor may not be possible. Surgical resection is considered by experts in the field to be the best option for initial treatment of the bleeding mass. Therefore, it is sensible to perform surgery in order to remove the tumor and formulate the diagnosis basing on the histopathological evaluation of the tumor tissue. Bleeding may also be caused by massive metastases. In said scenario, the surgery performed may not stop the bleeding. Due to said fact, it is strongly recommended to perform tests to assess the neoplastic disease stage before the surgery (thoracic radiographs based on three projections, abdominal ultrasound, and echocardiography). A primary care physician handling peritoneal bleeding should initially focus on stabilizing the patient by restoring its effective circulating blood volume and stopping the ongoing hemorrhage (Herold et al. 2008).

Intravenous fluid infusion, involving the administration of a fluid bolus of approximately 1/4 to 1/3 of the total blood volume over 15–30 min, may be taken advantage of to mitigate deficiencies identified. However, said approach can lead to the rapid redistribution of fluid into the interstitial space, leading to edema, hypothermia, and exacerbated bleeding. Yet another option possible is volume restriction (Hammond & Holm 2009). It involves using the smallest possible volume of fluid in order to restore intravascular volume and minimize interstitial fluid leakage. As a general rule, colloid or hypertonic fluid is combined with isotonic crystalloids, opting for smaller fluid doses (5–10 ml/kg) with continuous assessment of the patient

in order to reach mean arterial pressure of 70 mmHg or systolic blood pressure of 90 mmHg until definitive hemostasis is achieved, assuming that both cerebral and renal blood flow are preserved (Hammond & Holm 2009). Invasive blood pressure should be examined, because noninvasive measurements may overestimate blood pressure (Bosiack et al. 2010). The discussed method allows for a remarkably swifter stabilization of the patient, but rapid surgical bleeding control is vital to avoid organ dysfunction, as the patient's blood pressure is maintained at a lower level and hypernatremia caused by the hypertonic fluid may develop (Hammond et al. 2014).

A patient who does not respond to crystalloid or colloid fluid therapy, suffers from severe bleeding, or has a prolonged clotting time, should be given a blood product (Herold et al. 2008, Culp and Silverstein 2015). Blood transfusion is a treatment method that a physician may resort to during preoperative, perioperative, or postoperative period in order to stabilize a patient with intraperitoneal bleeding. Physicians taking advantage of said therapy should strive to maintain the patient's hematocrit above 25% (Culp and Silverstein 2015). If blood products or a donor are not readily available, yet another treatment option that can be utilized is autologous blood transfusion (ABT). Nevertheless, it is considered to be controversial due to the risk of hemolysis, coagulopathy, microembolism of fat or air, and the potential for malignant dissemination or bacteremia, leading to sepsis. In the course of routine transfusions, the blood product should not be warmed, but in the discussed scenario, it may be warmed in a temperature-controlled bowl (<39°C). Blood products should never be microwaved. Blood bags are connected to infusion sets that contain a built-in microfilter. Maximum sterility must be maintained during the procedure of connecting the bag to the tubing. Such products should be administered by means of gravity flow. The rate of transfusion should be mainly dependent on the circulatory status of the animal, with the initial rate of transfusion being remarkably low in order to allow for adverse reactions to be identified and taken care of as swiftly as possible. In order to reduce the risk of bacterial contamination, transfusion of a single bag should take approximately 4 hours. The volume of blood to be transfused should be dependent on the therapy being administered, anemia severity, blood product availability, and patient size. Several dosing formulas pertaining to said products have been created for both felines and canines. However, a convenient and quick conversion factor for the amount of blood to be transfused is the "rule of three ones": 1 ml of whole blood per lb (453 g) of body weight increases the hematocrit by 1%, or in other words, 2.2 ml of blood/kg of body weight increases Ht by 1%.

Forecasts after successful splenectomy are to a remarkable extent dependent on the underlying splenic disease. Long-term survival in the case of hemangiosarcomas is very rare, even while combined with adjuvant chemotherapy. Nevertheless, splenectomy may turn out to be the cure for other lesions. In one study (Cleveland et al. 2016), 74 of 105 (70.5%) patients had benign splenic lesions, whereas 31 (29.5%) had malignancy, with the most common one being hemangiosarcoma (18/31 [58%]).

SKELETAL CHANGES

Osteosarcoma is considered to be the most common primary bone tumor in dogs. Less typical primary bone tumors identified in canines include chondrosarcoma, fibrosarcoma, hemangiosarcoma, as well as histiocytic sarcoma (Withrow & MacEwen 2019). The most common area of osteosarcoma development in dogs is the metaphysis of long bones, with the most typical sites being distal radius and proximal humerus. Bone metastases may also occur either from osteosarcoma or from primary tumors developing in other organs. Most common areas of bone metastasis are vertebrae, ribs, humerus, and femur. It is worth noting at this point that animals with osteosarcoma have more vascular than lymph node spread, hence metastatic lesions are more frequently identified in the lungs (Hillers et al. 2005). Nevertheless, metastases of other cancer types within the skeleton are observed less frequently than primary bone tumors (Trost et al. 2014).

Pain relief should be the key point of focus of a primary care physician (Table 2). A multimodal approach to pain control provides synergistic analgesia while at the same time reducing the total dose of each analgesic, which results in fewer side effects being identified (Jin & Chung 2001). Ultrasound-guided sciatic, femoral, radial, and brachial nerve blocks may provide additional pain control under sedation or anesthesia, but the requirement of specialist equipment and experience may greatly limit the availability of the aforementioned options (Bhoi et al. 2012).

Hypertrophic osteopathy is an inflammatory condition that can be diagnosed in dogs with intrathoracic neoplastic disease. It is characterized by painful distal limb swelling and periosteal proliferation seen on radiographs (Salyusarenko et al. 2013, Witherss et al. 2015). Patients may suffer from respiratory distress due to intrathoracic lesions or signs of systemic inflammation (Witherss et al. 2015). Hypertrophic osteopathy most often occurs in the case of primary or metastatic pulmonary neoplasia. However, it may also be connected with extrapulmonary neoplasia, *Spirocerca lupi* granulomas, as well as lung diseases characterized by various infectious or inflammatory etiologies (Witherss et al.

2015). The diagnostic test of choice should be a distal limb radiograph accompanied by simultaneous chest radiograph (Lee et al. 2012). The resolution of the underlying disease in the thoracic cage should result in the resolution of clinical symptoms of hypertrophic osteopathy (Peeters et al. 2001, Witherss et al. 2015). The administration of anti-inflammatory medications may alleviate lameness, swelling, and pain in the distal limb, but it rarely ensures long-term relief (Salyusarenko et al. 2013). Hypertrophic osteopathy is a rare paraneoplastic syndrome identified in felines. One case of idiopathic hypertrophic osteopathy has been reported in a cat (de Melo Ocarino et al. 2006, Huang et al. 2010).

Feline lung-digit syndrome (FLDS) is a condition, in the case of which primary lung tumors lead to metastatic changes in one or more digits (Sugiyama et al. 2010, Goldfinch & Argyle 2012). Acrometastasis may be distinguished from hypertrophic osteopathy on radiographs. It is associated with bone lysis ± periosteal proliferation limited to second and third digit phalanges (Gottfried et al. 2000). In numerous scenarios, lung tumors are asymptomatic and can be diagnosed only after noticing digit-specific changes. Symptoms of digit changes include swelling, ulceration, purulent discharge, claw loss, as well as severe pain. More commonly, thoracic digits are affected. Most typical histological types of primary lung tumors responsible for lung-digit syndrome in felines include adenocarcinoma, bronchioloalveolar carcinoma, squamous cell carcinoma, and adenosquamous cell carcinoma (Thrift et al. 2017).

CHEMOTHERAPY-INDUCED EMERGENCIES

Chemotherapy is considered to be a relatively safe procedure, characterized by less than 25% of animals treated experiencing adverse symptoms (Withrow & MacEwen 2019), of which only 5% are life-threatening in nature. The 2021 consensus issued by the Veterinary Cooperative Oncology Group (VCOG-CTCAE v2) provided veterinarians with a grading scale for adverse events that may occur, as well as with comprehensive terminology in order to facilitate both accurate and consistent reporting of adverse issues regarding cancer patients. Such terminology standardization is essential for sharing vital pieces of information between clinicians. The terminology addresses a broad range of adverse events, categorized basing on anatomy or pathophysiology, with each event being graded from 1 (mild adverse event) to 5 (risk of death).

Gastrointestinal toxicity

Gastrointestinal disorders during chemotherapy occur less frequently in dogs

and cats than in humans. Two main causes of gastrointestinal toxicity in cancer patients can be identified: central vomiting due to the stimulation of vomiting center and peripheral vomiting resulting from direct effects on the gastrointestinal tract. Central nausea caused by chemotherapy appears rapidly during drug administration or within the initial few hours after administration. Said form of nausea is rarely an emergency and can typically be controlled with antiemetics, which should be administered prophylactically, before the administration of an emetogenic chemotherapeutic agent or additionally when nausea symptoms are observed. It is also recommended to administer medications that protect the gastrointestinal tract throughout the period of chemotherapy-oriented treatment. Those may include omeprazole or famotidine and sucralfate.

Decreased appetite, nausea, vomiting, and diarrhea are often identified as consequences of tumors that directly invade the gastrointestinal tract or cause external compression of either stomach or intestines. Said symptoms occur secondary to gastrointestinal obstruction, peritumoral inflammation, or affect gastrointestinal motility and absorption. The removal of the aforementioned disorders involves treating the underlying cause. It can be achieved by means of the surgical removal of the tumor or the reduction of tumor volume by opting for other treatments (such as chemotherapy or radiotherapy). Chemotherapy-induced gastrointestinal toxicity can also be identified as a result of direct toxic effect of the aforementioned medications on gastrointestinal cells. It usually appears 2–5 days after cytotoxic medication administration, so if gastrointestinal symptoms occur outside of this period, it is important to take into account other (non-chemotherapy-related) causes of their occurrence. The likelihood and severity of gastrointestinal disorders during chemotherapy varies, as it is dependent on chemotherapeutic agents utilized.

Animals may be fasted for several hours. However, they should be provided with water. Once vomiting has subsided, a light diet may be reintroduced (Vail 2009). Antiemetics may also be administered, preferably parenterally. Typically used antiemetics are maropitant and ondansetron (Vail 2009; Whitehead et al. 2016). Intravenous fluid therapy is recommended in the case of patients suffering from severe gastrointestinal side effects. A multimodal approach to antiemetic therapy may be additionally required with regard to such patients, as nausea may result from both peripheral gastrointestinal dysfunction and the stimulation of vomiting center.

Neutropenia

Neutropenia is considered by professionals in the field to be one of the

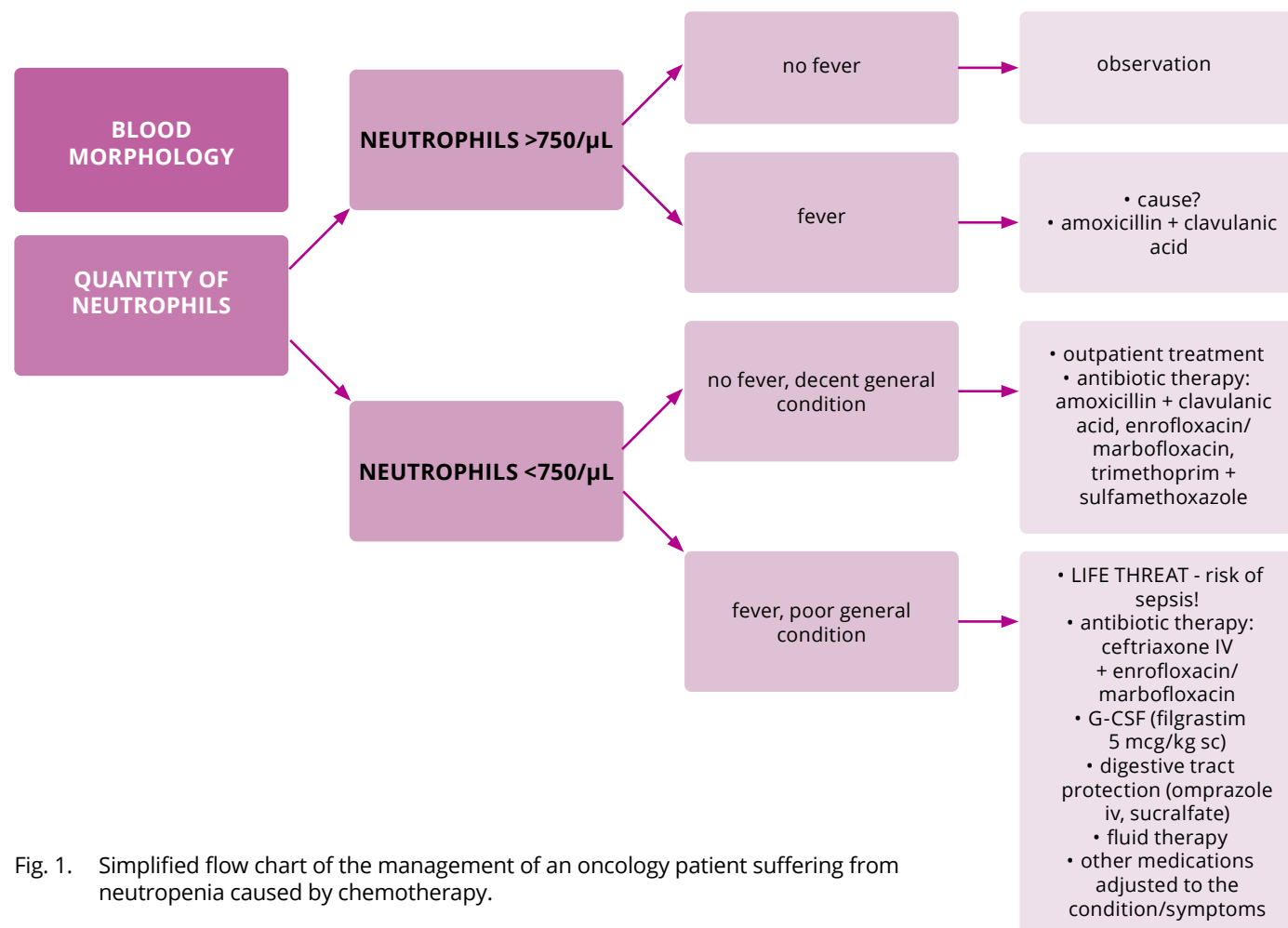


Fig. 1. Simplified flow chart of the management of an oncology patient suffering from neutropenia caused by chemotherapy.

most commonly observed chemotherapy-specific complications. Risk factors regarding the development of neutropenia in cancer patients depend on the type of cytotoxic therapy opted for, individual predispositions, as well as health status of the sick animal. Medications used as a part of chemotherapy are often associated with the development of neutropenia due to their myelosuppressive effects. Neutropenia classification in both felines and canines according to VCOG-CTCAE v2 for grade I is equivalent to or falls below the lower limit of the norm, up to 1500/ μ L, grade II is in the range of 1000-1499/ μ L, grade III oscillates around 500-999/ μ L, grade IV is below 500/ μ L, and grade V is equivalent to the death of the patient. Nevertheless, basing on the author's experience, clinical symptoms associated with neutropenia are not common unless the neutrophil count falls below the threshold of 1000/ μ L. In the majority of cases, post-chemotherapy neutropenia may be asymptomatic. That is why it can often go unnoticed or be detected during a blood count check-up or a check-up carried out before the next chemotherapy. However, it has to be mentioned that neutropenia may be accompanied by fever (body temperature above 39.2°C), as well as clinical symptoms of infection may be identified. Risk factors for the development of neutropenia in dogs after chemotherapy include lower body

weight and chemotherapy protocols that are designed with high-grade lymphomas/leukemias in mind. Moreover, the severity of neutropenia is dose-dependent, whereas its duration is correlated with the type of chemotherapy agent utilized. The currently used medications that are characterized by the most potent myelosuppressive effect are: doxorubicin, cyclophosphamide, vinblastine, mitoxantrone, and lomustine. Basing on the author's own experience, neutropenia may often occur after the administration of vincristine (Brown & Rogers 2001; Sorenmo et al. 2010, Pierro et al. 2016).

Patients with neutropenia may visit a veterinary clinic with various clinical symptoms, among which the most common ones are reduced appetite or weakness after chemotherapy. Symptoms of neutropenia may be more pronounced in the case of more intensive oncological therapy and more severe bone marrow failure caused by the underlying neoplastic disease. If said symptoms are diagnosed around the expected lowest neutrophil level after the recent administration of a cytotoxic medication (usually given 7-10 days after chemotherapy), especially with accompanying fever, febrile neutropenia should be considered. A blood count should be carried out in order to confirm and determine the severity of neutropenia. The method of managing patients suffering

from such medical conditions is presented in Fig. 1.

Septicemia may be identified in patients with severe neutropenia. Nevertheless, the incidence of sepsis caused by myelosuppressive chemotherapy in veterinary patients is relatively low and is likely multifactorial in character (Sorenmo et al. 2010). Untreated septicemia may be fatal. In patients with sepsis, it is vital to determine (if possible) the source of infection, which makes it possible to opt for the most effective therapy. Diagnostic tests, including thoracic and abdominal cavity imaging and/or taking blood and urine cultures, may help identify the source of infection. Blood samples for culture should be taken from multiple sites and be obtained before the initiation of antibiotic administration. Nevertheless, it has to be pointed out that such an approach may not be feasible in all veterinary patients (Dellinger et al. 2012). Once all the necessary diagnostic samples are collected, broad-spectrum antibiotics should be administered. Patients are typically treated with a beta-lactam combined with fluoroquinolone (Silverstein D. & Hooper K. 2022). A broad spectrum of activity is recommended, targeting both Gram-positive and Gram-negative microorganisms, with the inclusion of anaerobic bacteria (Laforcade et al. 2003, Silverstein D. & Hooper K. 2022).

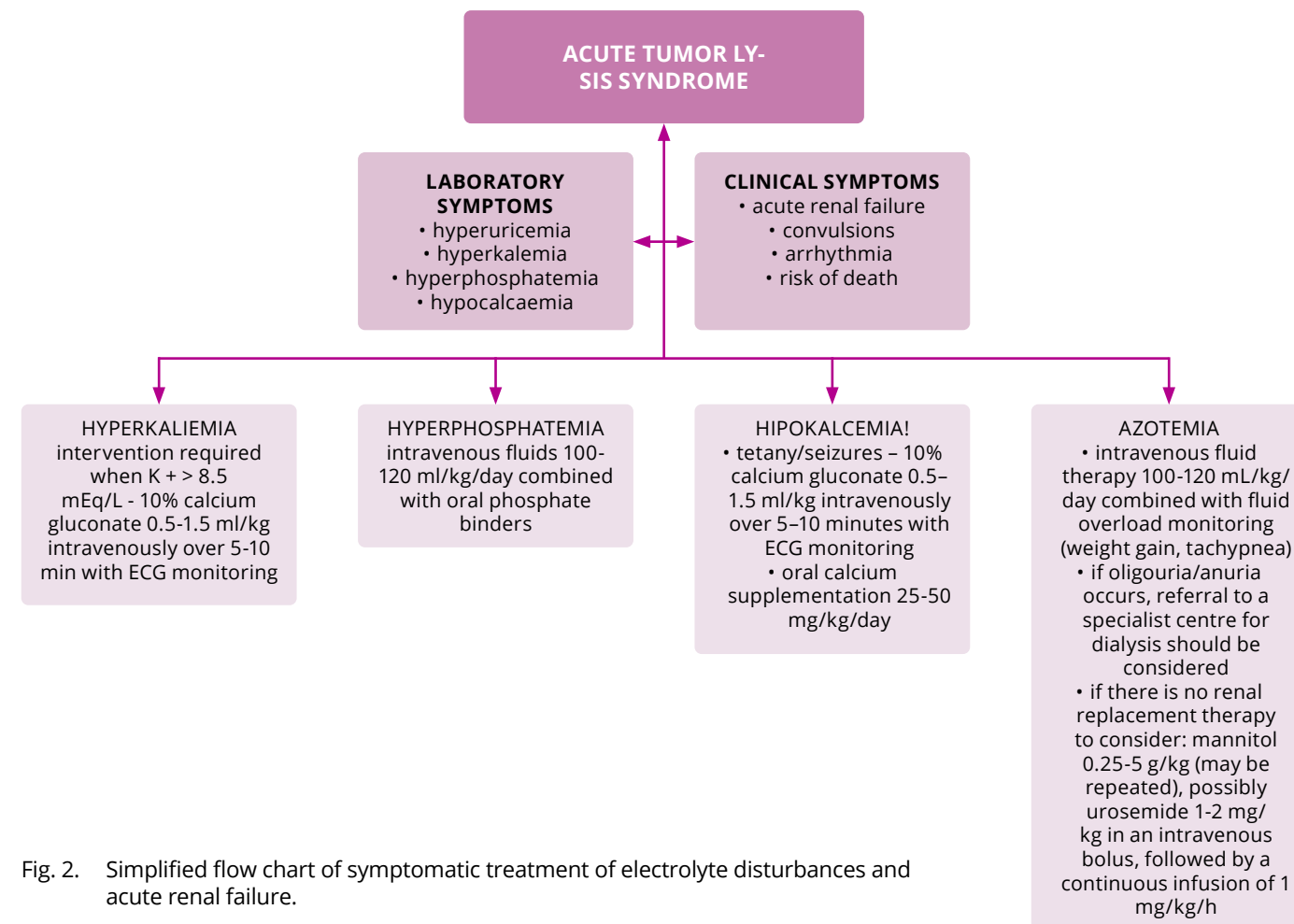


Fig. 2. Simplified flow chart of symptomatic treatment of electrolyte disturbances and acute renal failure.

Myelosuppression and its secondary complications are considered to be major dose-limiting toxicities related to chemotherapy, which may lower the overall effectiveness of the treatment in question. The utilization of recombinant G-CSF (granulocyte colony stimulating factor; it acts on neutrophil precursors in the bone marrow, boosting their maturation, proliferation, and neutrophil activity) has been shown to reduce both the severity and duration of neutropenia in human oncology patients. Even severe neutropenia generally resolves quickly as a result of G-CSF activity (Britton et al. 2014). Said fact is consistent with the author's experience. Due to the possibility of autoantibody formation, G-CSF should be considered in specific cases, especially when neutropenia is severe and long-lasting in character. The best way of avoiding neutropenia-specific complications is to prevent its development. Regular blood tests can help detect a leukocyte deficit in time, allowing for introducing an appropriate treatment.

ACUTE TUMOR LYSIS SYNDROME

Tumor lysis syndrome (TLS) is a group of disorders developing as a result of the rapid breakdown of cancer cells. It causes the release of large amounts of

substances that were previously located inside tumor cells. TLS occurs when a significant number of cancer cells are damaged and simultaneously release their contents (nucleic acids and various ions, including potassium and phosphorus) into the bloodstream. Such a state of affairs may lead to a strong reaction. Tumor lysis syndrome can occur spontaneously or, as it is the case more often, is a complication connected with anticancer treatment, which may accompany both general chemotherapy and targeted molecular medications. The spontaneous form of tumor lysis syndrome mainly affects dogs and cats suffering from lymphomas and leukemias. TLS may occur within the initial few days of medication administration, which may, for example, have the form of chemotherapy-specific infusion. It usually affects tumors that are characterized by the ability to rapidly divide cells and are highly sensitive to the type of therapy opted for, which are especially hematopoietic system tumors.

Metabolic disorders such as hyperuricemia (excess uric acid being the product of the breakdown of nucleic acids), hyperkalemia, hyperphosphatemia, as well as hypocalcaemia can be identified. Disturbances of the ion balance cause the precipitation of uric acid crystals in the kidneys and urinary tract. Deposits accumulated may destroy the structure

of urinary system organs, leading even to acute kidney damage (Mylonakis et al. 2007; Vickery & Thamm 2007). They may also cause seizures, arrhythmia, and - in extreme cases - death. Due to said fact, TLS requires rapid diagnosis and the immediate implementation of intensive treatment. The effective treatment of acute TLS depends on the symptomatic removal of electrolyte disturbances and the prevention/treatment of acute renal failure. Fluid transfusion and renal support play an important role when it comes to the treatment of TLS. It is vital to administer an appropriate amount of intravenous fluid to treated patients. Said approach helps remove harmful substances that have been released into the blood by tumor cells from the body. Supporting urinary toxin excretion protects patients against life-threatening complications. Initial guidelines for prescribing intravenous fluids incorporate the following formula: dehydration percentage x body weight in [kg] = fluid deficit in liters (Cavanagh et al. 2016). Even with careful fluid administration, patients are at risk of fluid overload, which is typically defined as fluid accumulation exceeding 10% of baseline body weight (Cavanagh et al. 2016). The development of overhydration and/or oliguria/anuria often points to the end-stage of acute renal failure. When it occurs, renal replacement therapy is considered the

Table 1. Palliative management of hypoglycemia caused by insulinoma.

MANAGEMENT OF HYPOGLYCEMIA		
diet	• small meals rich in proteins, fats, and complex carbohydrates; low in simple sugars • meals should be administered 4–6 times a day to prevent spikes in tumor insulin secretion and provide sufficient calories at frequent intervals	
prednisolone	0.5-6 mg/kg/day PO	glucocorticoids are utilized to increase blood glucose levels by causing insulin resistance and liver gluconeogenesis
diazoxide (Proglicem®)	10-40 mg/kg/day PO (daily dose should be divided into parts)	non-diuretic benzothiadiazine derivative, increases blood glucose levels by means of multiple mechanisms operating together
propranolol	0.2-1 mg/kg 3 times a day PO	enhances the hypoglycemic effect of insulin and oral antidiabetic medications
glucagon	0.03 mg/kg IV	works opposite to insulin, stimulating an increase in blood glucose levels
octreotide (Sandostatin®)	2-4 mcg/kg 2-3 times daily SC	somatostatin analogue causing hyperglycemia by inhibiting growth hormone, insulin, glucagon, and gastrin

gold standard of treatment. Nevertheless, its high cost and poor availability limit its use in veterinary medicine. If oliguria/ anuria occurs without haemodialysis, the chances of normalization are very low and the forecast for the patient is not optimistic. In the case of the refusal or unavailability of renal replacement therapy, vasodilators may in theory increase the glomerular filtration rate (Keir & Kellum 2015). In parallel, ionic imbalances in the body should be corrected in order to achieve the best result possible. The scheme presenting basic symptomatic treatment of electrolyte disturbances and acute renal failure is presented in Fig. 2.

The exact incidence of TLS in felines and canines is unknown. Nevertheless, basing on the author’s experiences, TLS can be incorrectly attributed to severe adverse events following chemotherapy that are unrelated to tumor cell lysis. If no characteristic electrolyte disturbances are observed or if there is no significant reduction in tumor volume, it is vital to consider other causes of the clinical symptoms identified. TLS is a life-threatening condition and should be treated as such. In order to

prevent severe consequences of tumor lysis, patients being at risk of developing said syndrome should be properly prepared before the administration of a valid dose of antineoplastic medication.

Closing remarks

Together with the expansion of treatment options for pet-specific cancers, general veterinarians can expect to see an increasing number of patients with complications related to both the cancer itself and its treatment. In said cases, care requires prompt diagnosis and appropriate therapy. Health concern management should include both discussions with the owner pertaining to goals he or she would like to achieve and communication with a veterinary oncologist aimed at maximizing treatment success. Even though few cancers can be completely cured by veterinary medicine, the treatment of some of said oncological complications can be effective and improve the quality of life of animals affected.

Table 2. Flow chart of a multimodal approach to pain control.

NON-STEROIDAL ANTI-INFLAMMATORY MEDICATIONS		OPIOID MEDICATIONS		SUPPORTING MEDICATIONS	
firocoxib	5 mg/kg/day	methadone	0.1-0.2 mg/kg every 6-8 hours	amantadine	3-5 mg/kg/day
meloksikam	0.2-0.05 mg/kg/day	buprenorphine	0.01-0.02 mg/kg every 4-6-8 hours	gabapentin	5-10-20 mg/kg every 8-12 hours
piroxicam	0.2-0.3 mg/kg/day	fentanyl	4 mcg/kg/h (transdermal system)	tramadol	2-4 mg/kg every 6-12 hours

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11

Diagnostics and treatment of most common heart tumors in dogs and cats

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Abstract: Cardiac tumors are considered by experts to be remarkably rare oncological diseases in dogs and cats. The heart muscle can serve as the major area of primary tumor development, as well as the destination of distant metastases, in both cases resulting in a varied clinical image, especially depending on the size and location of the lesion. Unlike other neoplastic diseases, the histological type seems to be of lesser importance than the size and location of the tumor. Even though some of heart-specific tumors may be notably malignant, such a state of affairs does not automatically indicate a better forecast in the case of patients with benign tumors. The performance of surgical procedures is often impossible, apart from interventional pericardiectomy, rare cases of small focal lesions located in the right atrial appendage, or cytoreductive procedures performed in the case of heart base tumors. Not much is known when it comes to the effectiveness of radiotherapy. What is more, said lesions are often resistant to chemotherapy, which is why it is rare to consider the probability of even a partial remission. Nevertheless, there are still many possibilities of providing care to cardio-oncological patients that can be taken advantage of. Pharmacotherapy for hemodynamic complications, attempting to improve the quality of life, as well as undertakings aimed at reversing clinical symptoms may bring the expected results, provided that they are applied in compliance with the properly done risk-benefit calculation. Ultimately, the devastating diagnosis of "heart cancer" may turn into a chronic disease, being an everyday companion of elderly canines and felines.

Keywords: angiosarcoma, heart base tumor, cardiac lymphoma, chemotherapy

Introduction

Cardiac tumors in pets are rather rare, as they do not exceed 4.5% of proliferative lesions identified in the case of both dogs and cats (1,2). The vast majority of diagnosed cases are primary tumors, whereas metastases to the myocardium constitute only 14% of proliferative lesions identified in the discussed area (3). Angiosarcoma is the dominant cardiac tumor in dogs, occurring only slightly more frequently than heart base tumors (such as chemodectoma, paraganglioma). Nevertheless, according to some experts in the field, it may constitute up to 69% of all cardiac tumors in dogs (4). Chemodectoma is a formation derived from chemoreceptor cells responsible for detecting changes in the partial pressure of carbon dioxide, oxygen, as well as pH fluctuations in arterial blood, in the aortic arch, and in carotid body, among others (5,6). Heart base tumors are characterized by a lower metastatic potential and occur more frequently than carotid body chemoreceptor tumors in dogs (7,8). Due to a remarkable similarity of the cytological image, which is predominantly connected with the common neuroendocrine origin, as well as with sharing a similar location, the final differentiation of chemodectomy from ectopic thyroid cancer can only be made basing on variations in the expression of specific markers identified during the immunohistochemical examination. Moreover, ectopic thyroid cancer does not exceed 1% of all heart tumors – it can therefore be said that it occurs much less frequently than chemodectomy (5,9,10).

Specific breeds have predispositions to

specific histological types of heart tumors being identified. While hemangiosarcoma is diagnosed mainly in breeds such as German Shepherds, Golden Retrievers, and Labrador Retrievers, chemodectomy is more common in brachycephalic breeds, including French Bulldogs, English Bulldogs, and Boxers (7). Chronic hypoxia and baroreceptors continuous stimulation are suspected to play a significant role when it comes to the pathophysiology of chemodectomy (5). Predispositions directly related to the genome and mutations present in the genetic material of the discussed canine group are also possible. Paraganglioma, nonpheochromocytoma, paraganglioma, and chemodectomy – all of these terms can be used interchangeably.

The two dominant histological types of cardiac tumors differ significantly with regard to their clinical behavior. While angiosarcomas are among more malignant tumors in both dogs and humans, with macro- or micrometastases at diagnosis in nearly 100% of patients, paragangliomas are usually benign and grow rather slowly. They rarely metastasize distantly, mainly to the lungs or myocardium (up to 30% of cases) (5,11), are much more often locally invasive (up to 43% of cases), and may occupy vital space to the detriment of surrounding healthy tissues, which is of remarkable importance in the case of closed anatomical structures limited by bone tissue, such as the thorax (11). Metastases from malignant tumors to the myocardium wall may occur in up to 36% of diagnosed dogs (12). In

felines, paragangliomas seem to be unrelated to the craniofacial structure (no increased predisposition has been noted in Persian cats, for example) and are slightly more aggressive, as distant metastases have been identified in almost half of the patients at the time of diagnosis (4,11,13,14). Benign myxomas are most common primary cardiac tumors in humans, whereas in pets, they are quite rare. Even though they can develop in most heart-specific anatomical structures, most cases have involved the tricuspid valve with the resulting expansion towards the right atrium or the right ventricular outflow tract (15,16). Myxosarcoma, the malignant counterpart of myxoma, can result in distant metastases to the lungs or myocardium, but said variant is extremely rare in felines and canines. In cats, the dominant cardiac tumor is lymphoma, which accounts for more than half of cases of heart tumors identified in the discussed species (17). Regardless of whether it develops only in the pericardial sac, is connected with the infiltration of the heart muscle by neoplastically transformed lymphocytes, or occupies both of said structures – in each case, it is referred to as "primary cardiac lymphoma", basing on the WHO guidelines for human medicine. Locations of heart tumor metastases range from the typical destination of most malignant changes in the body, namely – the lungs – to those less obvious ones, such as angiosarcoma, which is the most common metastatic tumor found in the intracranial area (18). Moreover, as many as 25% of dogs with a tumor in the right atrial appendage simultaneously show

focal changes in the spleen (being metastases of angiosarcoma). Conversely, up to 30% of dogs diagnosed with a splenic tumor also have changes in the right heart area. Nevertheless, it is not certain which location is primary in such cases and which is the focus of metastasis (19,20).

It should be taken into account that cancer is a risk factor for blood hypercoagulability. Therefore, episodes of thromboembolism in oncological patients may be expected. Cases of pulmonary embolism have been reported in patients with right heart myxosarcoma (16). Thromboembolism may be the main factor influencing the clinical image of the disease – for example: in the case of extensive pulmonary embolism in a French bulldog with chemodectomy, its presence resulting in an almost complete obstruction of the pulmonary artery trunk contributed to the lack of response to the introduced therapy and the development of permanent ascites, dyspnea, as well as of poor general condition due to anorexia and pain. All the factors have led to the decision to euthanize the pet in question (author's own observations, unpublished case). Interestingly enough, paragangliomas do not have to be a homogeneous and, as they are often called, benign group of neoplasms. There has been a case report identified of a hormonally active paraganglioma that was responsible for the induction of hypertension and atrial fibrillation due to its adrenergic activity. The fact that a significant proportion of patients with chemodectomy show the presence of metastases at the time of diagnosis indicates the potential aggressiveness of the discussed group. Therefore, there is still a remarkable, unfilled gap in knowledge pertaining to cardiac tumors in felines and canines.

Clinical symptoms

Patients often do not show any symptoms of cancer until its advanced stage, when

it is too late for an effective therapeutic intervention. Often, in as many as ¼ of patients with a heart base tumor, proliferative changes are diagnosed accidentally, during a preventive echocardiographic examination performed before anesthesia for rehabilitation or various orthopedic procedures (21).

Clinical symptoms, if they occur at all, may be of two types. On the one hand, they can be highly nonspecific, general symptoms that are difficult to link to a specific body organ or system, including dullness, appetite loss, excessive vomiting, exercise failure, or weight loss (15). Unfortunately, it may happen that the first and the last symptom is sudden cardiac death. More specific symptoms that direct diagnostic procedures towards the circulatory system (but do not exclude respiratory or neurological components) include dyspnea, cough, loss of consciousness, or ascites (1,3,5,15,19,22). Due to the risk of metastases to the central nervous system (identified in up to 30% of patients with angiosarcoma), maneuvering movements or head tilt may be observed (18,23,24). In dogs with a basal heart tumor, symptoms become apparent when the tumor reaches a size significant enough to cause a mass effect and exert pressure on structures surrounding the thorax (21). A severe, chronic pressure exerted on the intracranial vena cava reduces the preload of the right heart, ultimately leading to right heart failure. What is more, increased systemic vascular resistance causes effusions into body cavities and a reduction in the left ventricular ejection fraction.

In felines, recognizing initial symptoms of a tumor in the heart muscle area is even more troublesome. One can notice difficulties breathing, reduced plasticity of the cranial mediastinum, or excessive apathy of the pet. Interestingly, cough, overt dyspnea, or

cyanosis appear during final stages of the disease or not at all (11).

Clinical trial

From the pathophysiological point of view, hydrops in cats with pericardial lymphoma develops secondarily to impaired diastolic function with thickened epicardium, as well as due to reduced preload of the heart due to the compression of large intrathoracic vessels (13). Similar mechanisms can be also observed in dogs. Free fluid in the pericardial sac after the pressure inside the right heart chamber being exceeded leads to its compression, causing tamponade as a result. In such conditions, the preload of the right heart decreases, the output decreases, as well as right ventricular heart failure occurs. Clinically, fainting, exercise intolerance, and apathy may be observed. During the examination, muffled heart sounds, tachycardia, absent pulse, and mucous membrane pallor are noticeable. In the case of heart base tumors, which often exert pressure on the surrounding structures, the dilatation of jugular veins or even intracranial vena cava syndrome can be observed. Symptoms of left ventricular failure may occur when there is the compression of pulmonary vessels supplying blood to the left atrium.

Additional diagnostic-specific undertakings

Chest and abdominal imaging
Abdominal ultrasound examination may reveal ascites (starting from trace to severe one), dilated hepatic veins, and hepatomegaly secondary to intrahepatic venous congestion (1). Similarly, chest X-ray may support the diagnosis of a proliferative lesion in the cardiac region by detecting the presence of a mass effect. It typically has the form of the elevation of the trachea

Table 1.

Research item	Irregularities found	Pathophysiology/causes
Watching	Pale mucous membranes, shortness of breath	Decreased ejection fraction (5,18,19)
	Pelvic limb swelling	(Author's own observations)
	Jugular vein enlargement	Right ventricular heart failure caused by tamponade CVCS – mass effect, for example: in the case of HBT
	Venous pulse	
	Cranial Venous Syndrome (CVCS)	
Groping	Ascites	Hydropericardium, right ventricular failure (1)
Auscultation	Muffled heart sounds/breath sounds	Tamponade, attenuation of sound transmission through fluid (1,5)
	Tachycardia or bradycardia	Tumor infiltration of the cardiac conduction system, an additional symptom of congestive heart failure (5,17)
	Cardiac murmur	Turbulence of blood flow due to embolism/tumor/ external pressure (mass effect) (5)
Neurological examination	Consciousness disturbances, ataxia, walking in circles, lack of physiological nystagmus	Metastases in the CNS area (18)



and intracranial mediastinum widening, as well as cardiomegaly (7). Nevertheless, the aforementioned examinations cannot replace a professional assessment carried out by an experienced echocardiographer. Patients with cardiac tumors must be treated as oncological patients. Therefore, regardless of the low specificity and sensitivity of abdominal and thoracic imaging examinations during the assessment of the primary tumor, their performance is essential in the process of assessing neoplastic disease advancement and development. It is vital to exclude distant metastases, as well as additional organ changes that may affect the decision to start anticancer therapy. Cardiac troponin level assessment has turned out not to be helpful in diagnostics, unless there is the need to assess the degree of myocardial destruction (caused by severe arrhythmia or suspected concurrent myocarditis) or when diffuse neoplastic infiltration is suspected without the possibility of localizing the focal lesion during echocardiography-specific examination (17). Technetium labeling is useful only in the case of ectopic thyroid tumor diagnostics (3,25).

Cytopathological examination

Even though a large proportion of patients with cardiac tumors accumulate free fluid in the pericardial sac, said fact is not particularly useful with regard to diagnostics. Firstly, it usually contains a significant amount of erythrocytes, which leads to the dilution and "loss" of tumor cells that are exfoliated into the pericardial sac. Only effusions with < 10% of hematocrit may be useful diagnostically. Secondly, the cytological examination of the pericardial fluid is characterized by low sensitivity - false negative results can occur in as many as 74% of cases. Furthermore, in 13% of cases, there is the possibility of obtaining a false positive result! In total, 4 out of 10 patients with hydropericardium will have cancer. A similar percentage of patients will suffer from idiopathic pericarditis. Only the remaining dozen or so percent of cases will be cases, in which etiology should be sought in other non-neoplastic diseases, such as infectious, toxic, or traumatic ones (1,22,27). The appearance of the fluid is not characteristic and may range from heavily bloody modified exudate, through lymph (due to the obstruction of lymphatic vessels), up to straw-colored fluid (most often identified in patients with heart base tumors). Paragangliomas usually do not lead to bleeding into the sac, as is often the case with angiosarcomas that are highly sensitive to disruption, delicate, and macroscopically "gelatinous" (11). In patients with hydropericardium, differential diagnosis should always include primary circulatory system diseases, tumors, trauma, or issues being of idiopathic origin (11). While evaluating fluid sediment, it may be required to take advantage of immunohistochemical

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examination, especially when it is vital to differentiate adenocarcinoma and mesothelioma from reactive mesothelium that has a varying morphology due to irritation caused by the presence of fluid (22).

Regardless of the diagnostic value of body fluids, in the case of access being possible, fine-needle biopsy of the tumor mass should always be considered. As a general rule, it should be performed under general anesthesia or after pharmacological deep premedication (11).

Echocardiographic examination

Said examination is considered by professionals to be the most effective method of diagnosing cardiac tumors, as it is characterized by 100% specificity and 82% sensitivity in dogs with pericardial effusion (1,28). If the patient's condition makes it possible, a comprehensive examination should be performed before pericardiocentesis, as the fluid present in the pericardial sac provides natural contrast to focal lesions in the heart area (1,27). Angiosarcomas are usually located in the right atrial appendage (19). However, they can also inhabit all other available locations in said area (they can, for example, infiltrate left ventricular walls, interventricular septum, or even invade and organize at the heart base). It has to be mentioned at this point that such cases are rather rare (29). It may be, for example, a large mass irregularly demarcated from the adjacent myocardium, being heteroechogenic in nature, leading to the complete obliteration of the right ventricle and almost complete loss of the left ventricular lumen due to its excessive size. The lesion may be characterized by slightly higher echogenicity than the one identified in the case of the adjacent normal myocardium (18). Due to their high bleeding tendency, angiosarcomas are often accompanied by bloody fluid in the pericardial sac, often leading to a decrease in HCT, as well as to the development of tamponade. It may result in congestive right ventricular heart failure and/or arrhythmia (19). The diagnosis is often presumptive and based on the location (26) and ultrasound appearance of the lesion, as biopsy is quite frequently associated with high risk. What is more, due to the high blood content in tumor tissue, the examination made is usually non-diagnostic in character (1).

Unfortunately, the location and sonographic appearance are not always sufficient to offer a diagnosis, as both chemodectoma and angiosarcoma are highly vascularized tumors. Both tumor types can be located in the heart base area. Furthermore, one recent study has showcased that the tumor volume on transthoracic examination may be underestimated in up to 24% of cases (19,30).

Heart base tumor in canines

Chemodectomies usually are identified as extensive, strongly fixed masses at the base of the heart, often growing across the entire width of the mediastinum. Apart from the obvious mechanical effect on the heart, they simultaneously lead to severe compression/shifting of lung lobes located within the thoracic cavity. Smaller proliferative changes are often visible in the case of right parasternal vascular view (short axis) or PLAX view (long axis). Quite frequently, the presence of a large tumor mass leads to the compression of major pulmonary arteries (which secondarily leads to increased pressure inside the right ventricle), right atrium, intracranial vena cava, as well as to fluid accumulation, either in the pericardial sac or in the thoracic cavity (7). In some cases, free fluid can also be identified in the abdominal cavity, along with the dilatation of hepatic veins, caused by right heart failure (3). Even though chemodectomies are neuroendocrine tumors that are usually functionally inactive, cases of hormonally active paragangliomas have also been reported. Said lesions, located in the right atrium, have been associated with the occurrence of additional clinical symptoms secondary to adrenergic stimulation, including tachyarrhythmias (21,31). During echocardiographic examination, it is necessary to assess the effect on hemodynamics. For example, a lesion exerting significant pressure on the outflow tract from the right ventricle may increase flow velocity through the pulmonary artery. The pressure may also be directed at the pulmonary trunk or even at the bifurcation of main pulmonary arteries – both left and right one. The dilatation of hepatic veins, if not caused by tamponade, may be directly linked to the compression of the right ventricle by the tumor mass (3).

Heart base tumors in felines

Even though only 14 cases of feline heart base tumors have been reported in the literature of the subject, it can be concluded that they can assume all forms, shapes, appearances, and locations (32). Heteroechoic, multilobular lesions with soft tissue echogenicity have the capacity of infiltrating the interatrial septum (11), extending into the interior of the atria. Such location has not been observed frequently in dogs, but it has been reported. When it comes to the differential diagnosis in felines, such lesions should be connected with lymphoma, angiosarcoma, rhabdomyoma, heart base tumor (chemodectoma), myxoma, metastasis of cancer from a primary mammary gland, or lung tumor being considered. Among non-neoplastic lesions, thrombus, abscess, or inflammatory granuloma should be also taken into account (11). The recently published case of feline paraganglioma has been connected with an atypical primary

site, as it has most likely originated from *glomus pulmonare*. To date, one such case has been described in a dog (11,33,34).

Lymphoma in cats

Echocardiographic examination may reveal the hypertrophy of cardiac muscle walls and/or papillary muscles, as well as the increased echogenicity of said structures in relation to the normal heart image (17). Typically, neither left atrial enlargement nor simultaneous carriage of the FeLV virus is observed. In the current day and age, associations with viral etiology are being abandoned, especially since less than ¼ of feline patients diagnosed with lymphoma have had a positive test result (13).

Myxoma

The echocardiographic image of myxomas slightly differs from other heart-specific neoplastic lesions. As a general rule, irregular lesions can be identified, often characterized by remarkably differentiated echogenicity. The most common location of myxomas is the tricuspid valve, from which they can develop towards the right atrium and the right ventricle. Due to the location of the lesion, the tumor mass often disrupts free intracardiac blood flow, generating pathological pressure gradients inside the right heart and consequently preventing adequate filling of the right ventricle, similarly to tamponade. In some cases, areas of differentiation towards cartilage or bone tissue can also be identified in the tumor tissue, which can cast a shadow on chest radiographs (35).

Pericardial tumors

Neoplastic changes may directly and exclusively affect the pericardial sac, as it is in the case of mesothelioma, angiosarcoma, or lymphoma (1) (1,4). The pericardial sac may also be the area of development of metastases from other primary locations, which is the case when it comes to mastocytoma, mammary carcinoma, or lymphomas (both B- and T-cell ones) (1,36). Proliferative changes in the pericardial sac may have the form of thickening and increased echogenicity in a specific area (1). Even though the discussed changes may only affect a fragment of the pericardium, hemodynamic consequences may be consistent with generalized constrictive pericarditis, leading to the loss of left ventricular compliance and diastolic dysfunction (1,37). In said cases, it is vital to exclude other possible causes of the identified disorders, such as infectious, traumatic or idiopathic pericarditis, as well as changes caused by the migration of a foreign body. At the end of the list of differential diagnoses, a neoplasm should be included. It is caused by the fact that it is an unusual and rare location for primary tumors. Nevertheless, it is probable, especially when the thickness of the pericardial sac reaches excessive dimensions, up to several millimeters (13).

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3D echocardiography-based examination

Three-dimensional echocardiography allows for assessing the possibility of surgical resection and more precisely understanding the nature of the tumor, predominantly thanks to a better visualization of its vascularization. In some cases, it may grant more satisfactory results than computed-specific tomography (19). It allows for a remarkable visualization and differentiation of fixed elements of the tumor, as well as for the identification of mobile fragments, which may be thrombi accompanying proliferative changes (35).

Electrocardiographic examination

In patients with heart tumors, a whole range of different rhythm disturbances has been observed, oscillating from benign up to life-threatening ones. From severe bradycardias caused by damage to conduction pathways by neoplastic infiltration in the myocardial wall to galloping tachyarrhythmias, triggered, for example, by tumor hormonal activity (18). Among many different types of rhythm disturbances, the following have been observed: sinus tachycardia with ventricular complexes of <70 ms (19), ventricular and supraventricular extrasystoles, as well as those originating from the atrioventricular junction (1), ventricular bigeminy (18), atrioventricular dissociation (1), and complete atrioventricular block, either with or without ventricular escape rhythm (usually within the range of 20-50 bpm) (1,38). The infiltration of neoplastic cells may negatively affect atrioventricular node function, as reported in cases of angiosarcomas, paragangliomas, or lymphomas (29). Ventricular ectopy may be secondary to neoplastic infiltration. It may also result from the presence of ischemic areas (18,20,21). Moreover, even without clinically apparent arrhythmias, changes in the morphology of QRS complexes have been observed. They may indicate, among others, the infiltration of the right His bundle branch and its destruction, generating morphology consistent with its block (RBBB). Pauses lasting for more than 10 seconds have also been reported. They have been caused by the infiltration of neoplastic cells into pathways conducting electrical impulses in the heart.

Computed tomography (CT)

Even though said examination requires general anesthesia and is relatively expensive, it may be considered while assessing the possibility of surgical resection of the tumor. What is more, it is also an invaluable diagnostic tool in the case of a thorough evaluation of the pericardium, which may be enhanced by contrast in the case of tumor infiltration, thus allowing for a more in-depth assessment of tumor development and

the identification of potential metastases into the pericardial sac (1).

Furthermore, in some cases, said examination can be taken advantage of to achieve all the goals set during a single procedure (7). CT scan additionally allows for the identification of metastases in the myocardium, especially in cases of malignant tumors with a primary tumor in an extracardiac location with high metastatic potential (26). Yet another factor being in favor of performing CT is the preparation of the patient for radiotherapy. In some scenarios, the radiation field has to be extended beyond the primary tumor area, as it is the case, for example, while identifying lymphadenopathy that may indicate the affection of regional lymph nodes by the tumor (7).

Heart tumor treatment

Angiosarcoma

Surgical resection combined with adjuvant chemotherapy based on doxorubicin grants the possibility of prolonging the median survival time (MST) in dogs suffering from cardiac angiosarcoma (1,39,40). The forecast in patients without therapy opted for is dismal, with MST of only a few days. Furthermore, the resection of the pericardial sac alone does not significantly prolong survival, unless being combined with chemotherapy. It should also be taken into account that the epicardium is not removed in the case of pericardiectomy, mainly because of the high risk of inducing arrhythmia due to performing manipulations so close to the myocardium. The recurrence of hydropericardium and subsequent ascites may result from constrictive, exudative epicarditis that may be present even after pericardiectomy (41). On the other hand, it has been shown that the combination of surgery and appropriate chemotherapy allows for prolonging the median survival time to 6 months (19,42,43). Unfortunately, the VAC protocol recommended for patients with splenic angiosarcoma as an adjuvant after splenectomy has never been evaluated with regard to tumor being located in the right atrium or in the heart. Alternatively, monotherapy with IV doxorubicin at the dose of 30 mg/m² every 3 weeks, combined with metronomic therapy with cyclophosphamide (IV, at the dose of 30 mg/m² every 3 weeks) and nonsteroidal anti-inflammatory medications (19) has been used.

In one study evaluating the efficacy of radiotherapy in patients suffering from cardiac angiosarcoma, responses ranged from complete response (CR) to stable disease (SD). Regardless of the effect on the tumor mass itself, in all patients, the combination of radiotherapy, vinblastine, and propranolol has resulted in the regression of hydropericardium with progression-free survival (PFS) of 290 days and MST of almost a year (326 days exactly)



(44). In the case of the most recent study evaluating its efficacy in right auricular angiosarcoma, stereotactic radiotherapy has reduced the required frequency of pericardial punctures, reducing the rate of effusion accumulation (1.45).

Treatment of heart base tumors with the emphasis put on paraganglioma

When it comes to asymptomatic patients with a heart base tumor, it is recommended to perform follow-up examinations, preferably opting for computed tomography, every three to six months, in order to assess tumor growth rate (21). Rapid growth may indicate an ectopic thyroid tumor. Surgical intervention options include pulmonary artery stenting, pericardiectomy or cytoreductive surgery, with the last solution being rarely possible (5). In life-threatening situations (tamponade, severe dyspnea), basic and easy-to-perform therapeutic procedures that should be opted for are pericardiocentesis and/or abdominocentesis. For a long time, reports have been cited pertaining to beneficial effects of pericardial removal in terms of prolonged survival in patients with a heart base tumor, even in those without hydropericardium. Nevertheless, such observations have not been confirmed (5,7,21,46). It has to be noted that there is still a notable lack of randomized prospective studies on the discussed subject. All conclusions presented in the literature of the subject are based on retrospective papers, which have significant limitations by definition.

When it comes to the treatment of heart base tumors, thoracic irradiation has also been considered, especially with stereotactic radiotherapy (3,5). Radiotherapy is an attractive solution for such patients, as surgical options are usually remarkably limited (7,47). Tumors have clearly defined edges and can be easily demarcated from the surrounding healthy tissue. Furthermore, neuroendocrine tumors are characterized by their high radiosensitivity (7,48). By taking advantage of the dose of 30 Gy, PR could be achieved in ¼ of cases, with the stabilization of tumor growth (SD) in 60% of cases for almost a year (21). Angiosarcomas and myxomas are likely to be characterized by radioresistance (7,21,49). In another study, based on using both stereotactic and conventional therapy, response to irradiation has been achieved in 50% of cases, and in ¼ of them - stable disease (SD) conditions have been observed (7). Nevertheless, regardless of the absolute size of the tumor seen in the control imaging studies, clinical improvement has been noted in most patients. It has even included the complete elimination of arrhythmia! MST has been 785 days and the type of radiotherapy used has had no effect on patient survival, whereas patients with arrhythmia at diagnosis have had worse forecasts. It must also be mentioned that

response to radiotherapy (PR vs. SD; SD vs. PD) has been clearly correlated with MST – longest survival periods have been noted in canines with PR. In one case, by opting for conventional radiotherapy (total dose = 57.5 Gy), the reduction of clinical symptoms has been achieved for as long as 32 months (7,50).

While taking into account dogs experiencing clinical symptoms due to the presence of a heart base lesion, various potentially useful therapeutic regimens have been offered, being predominantly based on the utilization of tyrosine kinase inhibitors (especially toceranib) and cytostatic medications (cisplatin, doxorubicin, cyclophosphamide, and dacarbazine). Such patients resign from radiotherapy for various reasons: financial ones, logistical ones, or due to the high risk of repeated anesthesia. In humans with paragangliomas, no satisfactory response has been identified with regard to classic cytostatic medications: cisplatin, doxorubicin, cyclophosphamide, and dacarbazine (5,51).

When it comes to human medicine, tyrosine kinase inhibitors are the basis for neuroendocrine tumor treatment. Toceranib has antiangiogenic effects due to its ability to inhibit the VEGF-2 receptor for vascular endothelial growth factor and PDGF platelet-derived growth factor (3,52). In patients suffering from a heart base tumor, the response has been achieved in only 10% of cases when given at a dose of 2.3–3.2 mg/kg body weight on a Monday–Wednesday–Friday schedule. Nevertheless, it has to be pointed out that as many as 90% of patients have experienced significant improvement in the quality of life and withdrawal of clinical symptoms, including the withdrawal of hydropericardium. Every second dog has experienced mild adverse symptoms (diarrhea, neutropenia, vomiting, depigmentation of the coat, and weight loss). However, such symptoms have not exceeded VCOG grade 1 and 2 criteria (53). In the cited study, the median survival time of 823 days has been achieved, which has not been influenced by the presence of metastases at the time of diagnosis (5). Medications that act on the circulatory system (e.g. diuretics) can be withdrawn so as not to affect the objective assessment of the response to toceranib, but only in patients who are sufficiently hemodynamically stable (3). Toceranib is also well tolerated by cats. Its toxic effect is limited, in most cases (similarly to dogs), to mild gastrointestinal symptoms and myelosuppression (11,54). Hepatotoxicity in said species may be a slightly greater issue (54). Notably impressive effects have been achieved in dogs in the course of ectopic thyroid tumor treatment, where the response to toceranib has in many cases meant complete regression of the lesions (CR – complete response) (5,52). + author’s own observations.

Forecasts for patients suffering from paraganglioma are much more optimistic

than those specific for easily bleeding and extremely aggressive angiosarcoma. The median survival time in dogs is often more than two years (5,46,55). The scarcity of reports on paragangliomas in felines does not allow for a clear assessment of the nature of said tumors. Nevertheless, they seem to be slightly more aggressive when it comes to said species than in the case of dogs, which is connected with slightly worse forecasts. Periodic punctures and palliative therapy can prolong life to six weeks maximum (11). The removal of the pericardial sac or cytoreduction does not result in survival times exceeding 19 months (11,56).

Cardiac muscle lymphoma

Cardiac lymphoma should be treated systemically, just as in the case of any other tumor location. The therapy of choice in felines has the form of the COP regimen, being the equivalent of CHOP in dogs. It consists of vincristine, cyclophosphamide, and prednisolone, as well as excludes doxorubicin (H), which is highly nephrotoxic when it comes to the discussed species. One feline patient with pericardial lymphoma undergoing the Wisconsin-Madison regimen has achieved an impressive survival time of 750 days. On the other hand, cats with T-cell lymphomas, regardless of therapy introduced (chemotherapy, steroid therapy), have not lived longer than 10 days. While treating cardiac lymphoma in cats, L-asparaginase, methotrexate, doxorubicin, and cytarabine have also been taken advantage of (17).

Closing remarks

Even though rare and not being a major problem in most patients undergoing cancer therapy in oncology clinics, cardiac tumors in pets should not be underestimated. Both primary tumors and metastases to the heart muscle can have a significant impact on the quality of life of patients, determine the rationality of decisions regarding therapy of choice, as well as affect individual forecasts. There are no two identical cardiac tumors, because even though they lack great diversity histologically (they are most often angiosarcomas, paragangliomas or lymphomas, which cover approximately 90% of cases), clinically they showcase a whole range of symptoms and various hemodynamic consequences. In some scenarios, very large focal lesions are a relatively lesser clinical issue than small tumors located on the physiological path of electrical impulses in the heart and generating life-threatening arrhythmias. Furthermore, the treatment of cardio-oncology patients is not limited to oncological care only, even though it should be the basic approach. It is also necessary, regardless of the forecast and therapeutic options pertaining to the primary disease (heart cancer), to provide most comprehensive care possible for hemodynamics and to attempt to stabilize the circulation of patients so that they

can overcome challenges connected with anticancer therapy. Symptomatic treatment will in some scenarios allow them to fully enjoy the time they have left without having to suffer from exercise failure or weakness on a daily basis. Nevertheless, for the treatment to be consistent and less toxic for patients, it is vital to combine knowledge from both fields (cardiology and oncology) for the common good of doctors, caregivers, and – above all else – patients suffering from the conditions discussed within the scope of this paper.

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Cardiotoxicity of cytostatic medications and tyrosine kinase inhibitors

Part 1. Specificity and clinical diagnosis

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Abstract: Developments made in veterinary oncology allow for an increasingly more efficient treatment of cancer diseases in both felines and canines, as well as for obtaining greater survival times. Advanced therapeutic methods have been introduced into everyday veterinary oncology practices. They are based not only on the utilization of classic cytostatic medications, but also - on molecular therapy and megavoltage radiotherapy. It has to be noted that each of such anticancer treatment forms may pose the risk of heart muscle damaging. Even though anthracycline cardiotoxicity is widely known, numerous other frequently utilized active substances may lead to the development of hypertension, cardiomyopathy, arrhythmia, and even sudden cardiac death. Basing on studies on dogs, as well as extrapolating reports from human medicine and innovative studies on lab animals, it is possible to initially determine risk factors contributing to the development of cardiotoxicity in pets undergoing oncological therapy, as well as to establish reasonable guidelines for monitoring, preventing, and treating cardiovascular complications that are possible to implement in veterinary practice-specific conditions.

Keywords: cardiotoxicity, CTRCD, cardio-oncology

Introduction

Medical progress with regard to cancer treatment has led to a significant increase in the survival rate of oncological patients, while at the same time generating a new clinical problem, namely - cardiovascular complications in patients in remission, in the case of whom circulatory system diseases are currently the second most common cause of death (1,2). Conventional chemotherapy, as well as new targeted therapies, are connected with a remarkably high risk of cardiotoxicity, causing heart failure, left ventricular systolic dysfunction, hypertension, embolic episodes, coronary artery spasm, and arrhythmias. Radiotherapy also has a notable impact on the circulatory system. Patients after irradiation cycles, especially those exceeding the total dose of 30 Gy, may experience coronary artery disease, pericarditis (with or without free fluid), degenerative disease of atrioventricular valves or, similarly to pharmacotherapy - conduction disorders or arrhythmia (3,4). Mediastinal irradiation is also a known risk factor when it comes to the development of a specific type of radiotherapy-induced cardiomyopathy, as well as neuropathy and autonomic circulatory system dysfunction (4,5). Even though initially only anthracycline cardiotoxicity was known, together with the one related to the utilization of trastuzumab, currently in human medicine, there are over 9 (!) classes of active substances known, which - through different mechanisms - can lead to cardiovascular complications. Details are provided in Fig. 1 (6). In the 60s,

when speculations about the correlation between anticancer therapies and heart diseases first appeared, the concept of cardio-oncology was born. It was a holistic multidisciplinary approach to be applied in clinical practice (7).

Cardiotoxicity of chemotherapy

As of currently, the awareness of the cardiotoxicity of anticancer therapy has increased disproportionately to possibilities of early cancer detection and effective prevention. The basis of therapeutic regimens in pet oncology is still the utilization of cytostatic medications used for years, such as cisplatin, cyclophosphamide, and anthracycline antibiotics, all of which are characterized by a greater or lesser potential for damaging the circulatory system (8). Even though radiotherapy can be the only factor underlying the development of restrictive cardiomyopathy, its potential to sensitize cardiomyocytes to drug-induced cardiotoxicity, especially anthracycline-induced cardiotoxicity, should also be taken into account (9). Chest irradiation damages the endothelium of coronary vessels and - by increasing oxidative stress in cardiomyocytes - damages them.

Doxorubicin (DOX) and other anthracycline antibiotics

DOX is the first anthracycline obtained from the *Streptomyces peucetius* soil bacterium strain introduced into oncological treatment. It quickly became

clear that oncological patients taking DOX developed cardiovascular symptoms, the prevalence of which increased significantly when the cumulative dose of 400 mg/m² was exceeded, while at the dose of 700 mg/m² - they affected 18% of patients (7). Clinical symptoms may appear after several months, years, or decades after the conclusion of cancer treatment. Interestingly enough, in addition to its standard mechanism of chronic cumulative cardiotoxicity, DOX, in both humans and dogs, may cause acute damage to the heart muscle, even after a single dose (10,11). DOX acts by inhibiting the synthesis of DNA, RNA, as well as proteins. Its toxicity to the circulatory system can be divided into acute and chronic one, with the latter being dependent on the cumulative dose. The antitumor activity of anthracyclines is related to their total concentration in blood serum (area under the curve, AUC) and cardiotoxicity results mainly from the transient maximum concentration (C_{max}) of the medication in question. The mechanism of cardiotoxic action of anthracyclines was associated with the action of free radicals and disruption of the normal function of 2-β DNA topoisomerase (12). Mitochondrial damage resulting from the utilization of DOX may be exacerbated by the simultaneous use of lapatinib, which has the capability of changing the membrane potential of mitochondria, which was confirmed basing on the rat embryo cardiomyocyte cell line (13). The combination of both active substances significantly increased oxidative stress in cardiomyocytes, inducing ferroptosis in H9c2 cell line (13). Despite

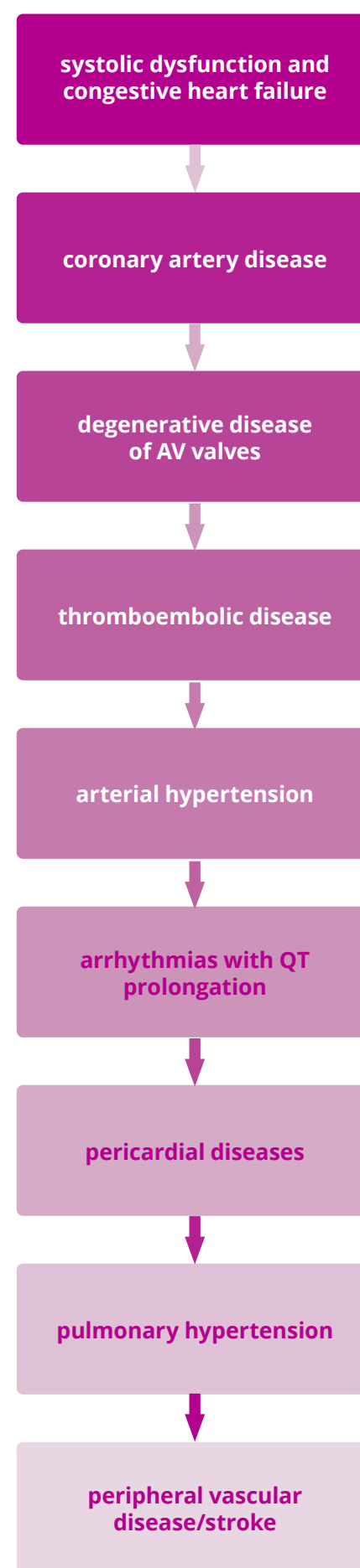


Fig. 1. Types of cardiovascular complications of anticancer therapy.

the obvious damaging effect on the heart muscle, due to its high anticancer activity, it is still one of the most commonly used cytostatic medications, considered the basis of treatment regimens for lymphomas, cancers, leukemias, and sarcomas in both canines and felines (14). In dogs, clinical signs of cardiotoxicity following DOX occur in no more than one-fifth of patients and are mainly arrhythmias. Much less frequent condition is the clinically overt congestive heart failure (CHF) (15). Epirubicin (EPI), a stereoisomer of DOX, has similar antitumor activity, but is also characterized by a significantly lower vascular damage potential (16). A case of dilated cardiomyopathy in a dog has been reported after EPI administration. Nevertheless, the discussed patient had previously taken six doses of DOX, reaching a high cumulative dose at which the risk of systolic dysfunction is remarkable. Therefore, it is not possible to clearly assess whether and which of said medications was ultimately responsible for the development of the DCM phenotype and for death being the result of the development of full-blown, therapy-resistant CHF (17).

Cyclophosphamide (CP)

CP belongs to the group of alkylating cytostatic medications interfering with DNA replication, as well as RNA transcription and replication, ultimately leading to the disruption of nucleic acid function (14). In the myocardium, it leads to cardiomyocyte edema and petechiae with the degeneration and necrosis of myofibrils. Even though the exact mechanism of CP damage remains unknown, similarly to DOX, oxidative stress and direct endothelial damage with leakage of proteins and toxic metabolites from the vascular bed to the intercellular space are suspected (18). Said changes lead to myocardium damage and the formation of microthrombi within its wall (18). CP causes the increased production of reactive oxygen forms, disturbs the redox balance, and generates lipid peroxidation in the myocardium tissue (19). At the same time, direct DNA damage, as well as the activation of 3 and 9 caspases occur. As a result, the mitochondrial pathway of programmed cell death (apoptosis) is initiated (20).

Cisplatin

Circulatory toxicity is the main adverse effect of cisplatin, limiting its use in oncology. It occurs as a result of mitochondrial dysfunction, dysregulation of redox balance, induction of mitophagy (mitochondria autophagy), and apoptosis (21). As a result of the damaging effect of cisplatin, intracellular enzymes of cardiomyocytes are released and the absolute heart mass increases. Furthermore, the concentration of angiotensin II, creatine kinase (CK), lactate dehydrogenase (LDH), and inflammatory mediators in blood

serum increases (22). Histopathological examination has revealed features of toxic damage to the heart muscle with disorganization of fibers, degenerated, pyknotic nuclei, and a significant increase in the share of collagen fibers in the structure of the myocardium. At the molecular level, there has been an increase in the percentage of p53 positive nuclei and increased expression of TNF-α. Ultrastructurally, mitochondrial swelling, disruption of myofibrils, and widening or even disruption of intercellular junctions between cardiomyocytes have been observed (23). Furthermore, a significant increase in lipid peroxidation, nitric oxide (NO) production, as well as notable reduction in glutathione concentration and the activity of the sodium-potassium ATP pump have been identified (24).

5-fluorouracil

Large-scale retrospective human medicine studies have indicated that clinically overt cardiotoxicity occurs in 1.3–4.3% of patients taking 5-FU (25). Even though the exact mechanism has remained unknown for quite a long time, coronary vasospasm has been suspected as the main cause of myocardial damage. Recent studies on a mouse model and cell lines obtained from the rat embryo have indicated the ability of 5-FU to induce ferroptosis in cardiomyocytes. What is more, the discussed medication has caused, similarly to CP, a significant increase in CK and LDH in the blood serum of the tested mice (26).

Paclitaxel

The discussed medication is taken advantage of in the case of human oncology in the treatment of breast tumors, transitional cell carcinoma of the urinary bladder (TCC), as well as prostate cancer (27). It has also been recently studied in the context of new therapeutic solutions in the treatment of liver cancers (28), canine melanoma in a mouse model (29), and angiosarcoma, showing high efficacy in the case of in vitro studies (30). When it comes to one of the latest studies assessing the efficacy of paclitaxel with regard to the treatment of neoplastic lesions in dogs, its cardiotoxic potential has not unfortunately been assessed (31). The medication in question has shown remarkable efficacy with the simultaneous occurrence of mild side effects, mainly in the gastrointestinal tract area (grade 1–2 according to VCOG-CTCAE) (32). When it comes to adverse effects related to the circulatory system, bradycardia has been noted in patients, usually asymptomatic one, which has not required pharmacological intervention (33).

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKI) are molecules that block the activity of kinases involved in the growth of cancer cells and

the process of angiogenesis, which is the creation of new blood vessels supplying the tumor. Due to their universal structure, some of active substances are able to inhibit a dozen or even several dozen different kinases, such as sunitinib or sorafenib, which is crucial in human medicine (34). Said compounds with many different targets, including those capable of blocking signals induced by vascular endothelial growth factor (VEGF) are responsible for clinically proven cardiotoxicity of TKIs. It includes: damage to the vascular endothelium, vasoconstriction, as well as increased blood coagulation resulting in thromboembolic episodes. Cases of CHF have also been reported in human medicine. Pathomechanisms being the source of these phenomena result from the fact that the signaling pathways involved in myocardial remodeling and those responsible for growth and angiogenesis in tumors are extremely similar (35–37). As it has been shown by recent studies, the impairment of contractile function results from a decrease in calcium concentration in the endoplasmic reticulum, as well as from the slowdown in calcium ion transport within cardiomyocyte fiber contractility compartments (38). Toceranib is commonly used off-label in pet oncology when it comes to the treatment of thyroid cancers (39), heart base tumors (40), gastrointestinal tumors (41), as well as inoperable mast cell tumors, for which it was originally studied (42). Among various studies in veterinary medicine, grade 1 and 2 hypertension according to the VCOG-CTCAE criteria has been found in 7 to 37% of dogs. Proteinuria (grade 1–3) has been identified in 7 to 26% of canines in the study group (39,41,43). Nevertheless, there have been no reports of systolic dysfunction after TKI use in pets.

Symptoms of cardiotoxicity in dogs and cats

The very first protocol developed to standardize the monitoring of patients undergoing oncological treatment in the context of heart diseases was developed at the turn of the 1970s and 1980s. It was based mainly on the assessment of the left ventricular ejection fraction, LVEF (44). Cancer therapeutic-related cardiac dysfunction (CTRCD) is defined as the reduction in LVEF by 15% of the baseline value or 10% below 53% (lower norm limit). It has been confirmed by a follow-up examination within 2-3 weeks (45). Even though the cardiotoxicity of chemotherapy may affect both the right and left ventricle equally, it has not been confirmed that right ventricular cardiomyopathy has had an adverse effect on the average survival time of patients who have managed to win the fight with cancer. When it comes to veterinary medicine, the Veterinary Co-operative

Oncology Group issued a consensus on common terminology criteria for adverse events of chemotherapy, which established clear rules for describing clinically apparent side effects of cytostatic medications on the circulatory system, including episodes of thromboembolism – showcased in detail in Tables 1.a. and 1.b. (32).

Post-anthracycline toxicity may occur during intravenous infusion of the medication or within hours or days after its administration. It usually manifests itself as a sudden onset of arrhythmia or episodes of hypertensive crisis. In severe cases, it may lead to cardiac arrest (14). One of the most extensive and recent studies assessing the risk of clinically overt anthracycline cardiotoxicity in a population of dogs undergoing chemotherapy has shown that 4% of canines developed clinical signs of circulatory failure, including sudden cardiac death (46). The mean time to the occurrence of symptoms such as fainting, weakness, apathy, exertional failure, or dyspnea was 194 days after the first dose of DOX, ranging from 50 to 928 days. The mean survival time after symptom occurrence was only 29 days, ranging from 0 to 913 days (46). In general, dogs are considered more sensitive to cardiotoxic effects of DOX than humans, in the case of whom symptoms of myocardial damage occur only after exceeding the cumulative dose of 550 mg/m², while in dogs they have been noted already at doses slightly exceeding 120 mg/m². Furthermore, the occurrence of individually variable sensitivity to damaging effects of anthracyclines has been confirmed, both in canines and in human patients (11).

In humans, after CP administration, cases of pericarditis (47, 48) and sudden cardiac death have been reported after a single dose (49). Electrocardiographic examinations have allowed to identify low-voltage recording, whereas echocardiographic analyses have revealed a significant thickening of the myocardium, increased echogenicity, systolic dysfunction, and free fluid in the pericardial sac (49). When canines with angiosarcoma undergoing chemotherapy with the VAC therapeutic regimen based on DOX, vincristine, and CP are concerned, 3 out of 15 dogs have experienced cardiotoxicity at cumulative doses of DOX not exceeding 150 mg/m² (50). Interestingly enough, two of them have been representatives of breeds included in the study by Hallman et al. (2019) being predisposed to the development of DCM - the Irish Wolfhound has developed AF with FS% - 27 and the Doberman Pinscher - VPCs with a decrease in FS% from 33 to 26%. In the latter case, premature atrial beats have been noted with a dramatic decrease in the fractional shortening to the level of 11.8% (50). A case of sudden cardiac death in a German Shepherd after 6 administrations of doxorubicin and cyclophosphamide has also been described in the literature. The patient

has shown symptoms of general weakness. What is more, atrial fibrillation has been found during the clinical examination (11). Histopathologically, features of subacute or chronic form of cardiomyopathy have been confirmed, with vacuolar degeneration confirming the picture typical of anthracycline cardiomyopathy (11).

Chest pain, palpitations, dyspnea, and hypotension have been reported in humans following the administration of 5-FU (25). Up to 2% of patients may experience severe cardiovascular complications, including massive myocardial infarction, cardiogenic shock, and ventricular asphyxia. The occurrence of any of the above symptoms precludes the further use of 5-FU in a given patient.

In the case human oncology, the utilization of TKIs has been associated with adverse events, such as hypertension and congestive heart failure caused by left ventricular systolic dysfunction or QT prolongation (51). Interestingly, the degree of QTc prolongation has not been found to correlate with the risk of torsade de pointes (TdP) and sudden cardiac death (51). The latest medications quite frequently used in canine and feline oncology include cytarabine and cytosine arabinoside. Both of them have a tendency to cause pericarditis in humans, fortunately responding well to symptomatic therapy based on steroids (52–54). When it comes to the population of dogs receiving toceranib, grade 1 and 2 hypertension according to VCOG-CTCAE criteria has been noted (ranging from 7 to 37% depending on the study), as well as grade 1 to 3 proteinuria in 7–26% of treated canines (39,41,43). In felines, cardiovascular complications associated with the use of toceranib are not frequently reported, mainly due to the lack of registration of the medication for the species in question. One of the available studies has indicated a possible role of said medication in the induction of congestive heart failure in a cat. However, the patient has not undergone an echocardiographic examination before starting the therapy. Therefore, it is not certain whether it has not been asymptotically ill with hypertrophic cardiomyopathy, which – regardless of the type of treatment applied – would have progressed spontaneously, causing circulatory failure and consequently – the death of the animal (55).

As of currently, the only cytostatic medication associated, apart from coronary artery disease, with the induction of drug-induced hypertension is cisplatin (22). In pets, no cases of hypertension have been reported after the administration of cisplatin.

Table 1.a. Criteria for the assessment of cardiovascular complications of chemotherapy in pets: general adverse events related to the circulatory system (32). In the case of each category of adverse events, grade 5 is equivalent to death, according to VCOG-CTCAE guidelines.

Adverse reactions related to the circulatory system	Grade 1	Grade 2	Grade 3	Grade 4
Acquired degenerative disease of atrioventricular valves	Thickening of atrioventricular valves without the need for treatment	Moderate regurgitation or stenosis, no treatment required	Severe regurgitation or stenosis, controlled with medications	Life-threatening, poorly responsive to therapy
CPA	-	-	-	Life threatening
Infective endocarditis	-	-	CHF or arrhythmia responding to pharmacological intervention	Severe or recurrent CHF; life-threatening arrhythmias: VT, AVB III
Left ventricular diastolic dysfunction	Asymptomatic, no need for intervention	Asymptomatic requiring pharmacological intervention (such as LA dilatation)	Symptomatic CHF responding to therapy	Recurrent, unstable CHF without response to treatment
Left ventricular systolic dysfunction	Asymptomatic, resting EF 45-50%	Asymptomatic, resting EF 40-45%	Symptomatic, responding to treatment: EF 20-40%	Recurrent CHF not responding to treatment EF <20%
Myocarditis	-	-	CHF responding to treatment	Severe, recurrent CHF
Hydropericardium	-	Asymptomatic	Tamponade	Life threatening
Pulmonary hypertension, PHT	-	Asymptomatic	Fainting, ascites, exercise failure, responds to therapy	Ascites, syncope, exercise intolerance refractory to therapy or poorly controlled
Sinus bradycardia	Dog < 60 bpm Cat <140 bpm	< 40 bpm < 120 bpm	< 30 bpm < 100 bpm	< 20 bpm < 80 bpm
Sinus tachycardia	Dog >140 bpm Cat >220 bpm	>180 bpm >230 bpm	>200 bpm >240 bpm	>240 bpm >260 bpm
Hypertension (>160 mmHg)	Asymptomatic, transient <24h, not requiring treatment	Recurrent or persistent >24h, therapy indicated	Requires >1 medication for effective control	Life-threatening (hypertensive crisis)
Hypotension (BP < 100mmHg)	Asymptomatic, transient <24h, not requiring treatment	Short-term fluid replacement therapy without hemodynamic consequences	Long-term therapy, without long-term consequences	Shock
Other	Asymptomatic or with mild symptoms	Moderate, requiring little intervention	Severe or requiring hospitalization, but not life- threatening	Life-threatening, requiring urgent intervention
Thrombosis	-	Deep vein thrombosis without the need for intervention	Deep vein thrombosis requiring intervention (anticoagulation)	Life-threatening pulmonary embolism, femoral artery embolism, etc.

Risk factors for chemotherapy-induced cardiotoxicity

In one of the most extensive studies pertaining to veterinary medicine and assessing the risk of post-anthracycline cardiotoxicity in dogs, the age of the

patient, intervals between cytostatic drug administrations (14 days vs. 21 days), total number of administrations, duration of infusion (1 h vs. 15 min), concurrent use of other active substances with known cardiotoxic potential, and concurrent chest irradiation have not been found to be to a significant degree correlated with an increased risk of myocardial damage or

the occurrence of clinical cardiotoxicity symptoms (46). Nevertheless, a significantly increased risk of adverse effects of chemotherapy related to the cardiovascular system has been demonstrated in dogs with a breed predisposition to DCM, in which clinical symptoms have developed during oncological treatment in as many as 15.4% of patients, compared to 3.0% of the

Table 1.b. Criteria for the assessment of cardiovascular complications of chemotherapy in pets: arrhythmias (32). In the case of each category of adverse events, grade 5 is equivalent to death, according to VCOG-CTCAE guidelines.

Rhythm disturbances	Grade 1	Grade 2	Grade 3	Grade 4
Supraventricular and AV junction arrhythmias: sinus tachycardia, APCs, bigeminy, atrial trigeminy, focal atrial tachycardia, OAVRT, PJRT, atrial fibrillation/flutter, atrial parasystole, JPCs, JT, others	Asymptomatic, does not require intervention	Pharmacological intervention is not required	Not fully controlled pharmacologically or controlled by implantable devices, such as pacemaker	Life-threatening (coexisting CHF, hypotension, collapse, shock)
Bradyarrhythmias, such as sinus bradycardia, sinus arrest, SSS, atrial standstill, sinoventricular rhythm, ventricular asystole, cardiac arrest, PEA, electrical-mechanical dissociation				
Conduction disorders: AVB, atrioventricular conduction disorders, BBB, others				
Ventricular arrhythmias: VPCs, bigeminy, trigeminy, accelerated idioventricular rhythm, monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, R on T phenomenon, Torsade de pointes, ventricular fibrillation, ventricular parasystole, others				

remaining canines (being outside the risk group for developing DCM). Moreover, as a result of the cited study, prognostic factors have been distinguished that allow for the prediction of the occurrence of clinically overt cardiotoxicity: a decrease in FS% after

the 5th dose of DOX and the occurrence of VPCs in the ECG examination have been statistically significantly correlated with the occurrence of myocardial damage in the multivariate analysis (p – 0.04, p – 0.008, respectively). It should be remembered

that myocardial damage alone after the use of DOX may be responsible for 2% of deaths in oncological patients, regardless of the degree of response to chemo- and/or radiotherapy of their primary disease (46).

Table 2. Imaging methods used in human medicine for diagnosing chemotherapy-induced cardiotoxicity – comparison and characterization.

Diagnostic method	Rated parameters	Method benefits	Method disadvantages + notes
Classic transthoracic echocardiography (TTE)	Assessment of left ventricular systolic function: LVEF%, MAPSE; Assessment of right ventricular function: TAPSE, RV fractional area shortening, tricuspid regurgitation (velocity), for example in patients taking TKIs Assessment of diastolic function: E/A wave ratio, left ventricular isovolumetric relaxation time, IVRT;	Easily accessible Inexpensive Safe Does not require patient sedation	Low accuracy Low repeatability (depending on the examiner and the equipment used) Changes can only be detected after myocardial damage has occurred (relatively late)
Tissue Doppler Imaging (TDI)	- Tissue Doppler in RV + LV; <i>peak systolic velocity of the mitral annulus</i> (s') →DTI; Strain imaging and tissue velocity index are capable of detecting changes in systolic left chamber function up to 3 months before decreased LVEF in echo; It describes myocardial deformation as a % of the baseline length during the cardiac cycle. <i>Strain rate</i> is the deformation rate/second, which can be measured in longitudinal, radial, and circumferential directions;	Detects changes earlier than standard echocardiography No anesthesia required	Better measurement repeatability than in the case of classical methods (56); lower availability
Cardiac Magnetic Rezonanse (CMR)	The gold standard in assessing left ventricular function, a necessary test before deciding to prematurely terminate chemotherapy due to its cardiotoxicity (57) It allows for the assessment of systolic and diastolic function, myocardial structure and valve function; it also allows for the assessment of pericardial thickness, the presence of fibrosis/scarring in the myocardium, and the presence of neoplastic infiltration; it also makes it possible to detect myocardial edema due to acute inflammation after anthracycline administration. (58)	No exposure to harmful radiation	High test cost, difficult to access, requires general anesthesia in pets It cannot be used in patients with an artificial pacemaker.
Computed tomography (CT)	Allows to assess LVEF, valve and pericardium structure, and the risk of coronary artery disease; Utilized especially during therapy with 5-FU, TKI, cisplatin	Better availability than MRI	High doses of radiation, requires the use of contrast, less accurate at high HR

Diagnostics of cardiovascular complications of anticancer therapy

Imaging is the basis for diagnosing changes underlying clinically presented cardiotoxic symptoms, as well as for detecting subclinical circulatory disorders. A detailed description of the specificity, advantages, and disadvantages of each of key diagnostic method available in the case of veterinary medicine is included in Table 2.

In the case of human medicine, standard echocardiographic examination is increasingly being replaced by more advanced methods, such as the analysis of myocardial strain by means of acoustic marker tracking in the assessment of global longitudinal strain (GLS). In simple terms, it is the mean change in the length of the left ventricle in the apical longitudinal direction, where measurements are made in the apical two-, three-, and four-chamber projections. Said indicator has been proven to be the most sensitive in the early diagnosis of anthracycline cardiotoxicity in humans. What is more, it has been proven that a 15% decrease in GLS from the initial value is considered pathological and suggests damage to the myocardium (10). In veterinary medicine, two-dimensional assessment of myocardial deformation by acoustic marker tracking (2D-STE, speckle tracking echocardiography) for the assessment of systolic function obtained from measurements made on healthy Dobermans has been taken advantage of (59). The average of the measurements obtained from the two-, three- and four-chamber views should serve as the basis for the assessment of left ventricular systolic function. It is also possible to utilize measurements from the GLS examination in the apical four-chamber view only, because the results do not differ significantly from each other (59).

Right ventricular assessment

2D STE has also proven to be exceptionally useful when it comes to assessing regional and global myocardial deformations by means of examining the strain and its frequency in relation to right ventricular systolic function. Moreover, said measurements are independent due to the influence of chamber geometry and the angle of examination of the specific structure (60). Right ventricular transverse strain and its frequency decrease with the progression of pulmonary hypertension. However, it has to be mentioned that the discussed advanced diagnostic methods have not been shown to be superior to standard echocardiography in the diagnosis of PHT (61). Magnetic resonance imaging studies have shown that cytostatic drug-induced cardiotoxicity manifests itself in the right heart more mildly and progresses

more slowly than the one in the left ventricle (62). MRI allows for an earlier detection of anthracycline cardiotoxicity symptoms compared to standard echocardiography and its more advanced modifications, such as TDI (62). While assessing patients with lymphoma undergoing multidrug chemotherapy using, among others, anthracyclines and cyclophosphamide, by opting for 3D echocardiography, it has been shown that the assessment of the right ventricular ejection fraction (RVEF%) and the change in the right ventricular end-systolic volume (RVESV) have been useful when it comes the diagnosis of chemotherapy-induced cardiotoxicity (63).

Utilization of myocardial damage biomarkers

Inhuman medicine, the lack of correlation between serum troponin T concentration and the decrease in LVEF% in patients after the administration of cytostatic medications characterized by cardiotoxic potential have been demonstrated. Highly sensitive tests assessing subtle changes in cTnT have allowed for the detection of cardiomyocyte damage before the obvious change in ejection fraction visible in imaging (64). Even though the assessment of troponin T or troponin I concentration has long been a known marker of myocardial damage, due to its low sensitivity in cardio-oncology patients, new diagnostic markers are still being considered. The latest reports indicate the potential use of, inter alia, S100A1 or microRNA, such as miR-502 (65,66).

Studies in canines have shown that the E/A wave ratio decreased with the administration of DOX and the concentration of troponin I in blood serum increased. Even though the study has been conducted on a small number of patients (n=13), and doses of DOX opted for have not exceeded the cardiotoxicity threshold (150 mg/m²), said results point to the possibility of assessing said parameters while examining the risk of myocardial damage. Nevertheless, there is no certainty about the existence of a correlation between the increase in said parameters and the development of clinically overt symptoms of circulatory system damage. Tater et al. (2017) reached similar conclusions, indicating that the utilization of DOX in standard doses does not necessarily have to lead to an increase in the concentration of biomarkers of myocardial damage or changes in imaging studies, and thus does not generate clinically significant cardiotoxicity in veterinary patients (67).

Interestingly enough, in the case of 5-FU-induced cardiotoxicity, the mechanism related to coronary vasoconstriction has not been confirmed in rat studies. Examinations are still ongoing to determine causes of its damaging effect on the circulatory system. In the case of said medication, NT-proBNP

proves helpful in detecting early signs of myocardial damage. However, further studies pertaining to the target species are still required (68). NT-proBNP, similarly to troponin I, may be characterized by species-dependent pharmacokinetics and pharmacodynamics, which may have a significant impact on the blood collection schedule when assessing patients exposed to the cardiotoxic effects of cytostatic medications (69). It also shows that different active substances that damage cardiomyocytes by different mechanisms may require separate diagnostic tests for early detection of toxic effects on the circulatory system.

Closing remarks

Despite the uncertain clinical significance, there is undoubtedly the risk of cardiotoxicity in dogs and cats undergoing anticancer therapy. In the future, veterinarians specializing in specific fields of clinical science will be required to consider the complex problems of geriatric patients who, due to the rapid development of diagnostic and therapeutic methods, can live with cancer for a long time, with the medical condition in question becoming yet another chronic disease. As of currently, there are decent technical and substantive foundations. Risk factors and medications characterized by the greatest cardiotoxic potential while used in pet oncology have been established. Nevertheless, new, more sensitive diagnostic parameters are still being identified that can detect circulatory disorders before they become serious and irreversible. By the time patients present clinical symptoms, it is usually too late for effective intervention, which is why it is so vital to focus on subtle signs of possible side effects of cytostatic medications. The next part of this paper is going to discuss methods of prevention, treatment, and monitoring of cardio-oncological patients in the field of pet medicine.

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Cardiotoxicity of cytostatic medications and tyrosine kinase inhibitors

Part 2. Monitoring, cardioprotection, and therapy

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Abstract: Developments made in veterinary oncology allow for an increasingly more efficient treatment of cancer diseases in both felines and canines, as well as for obtaining greater survival times. Advanced therapeutic methods have been introduced into everyday veterinary oncology practices. They are based not only on the utilization of classic cytostatic medications, but also - on molecular therapy and megavoltage radiotherapy. It has to be noted that each of such anticancer treatment forms may pose the risk of heart muscle damaging. Even though anthracycline cardiotoxicity is widely known, numerous other frequently utilized active substances may lead to the development of hypertension, cardiomyopathy, arrhythmia, and even sudden cardiac death. Basing on studies on dogs, as well as extrapolating reports from human medicine and innovative studies on lab animals, it is possible to initially determine risk factors contributing to the development of cardiotoxicity in pets undergoing oncological therapy, as well as to establish reasonable guidelines for monitoring, preventing, and treating cardiovascular complications that are possible to implement in veterinary practice-specific conditions.

Keywords: cardiotoxicity, CTRCD, cardio-oncology

Monitoring

In compliance with recommendations typical for human medicine, each oncological patient should undergo an assessment of the circulatory system before starting chemotherapy, as well as after its completion and six months later in the case of receiving the cumulative dose of <240 mg/m² of doxorubicin. After exceeding said dose, an examination is required before each and every subsequent dose (50 mg/m²) being administered (1). Extrapolating the above recommendations to veterinary medicine, the threshold value should be equal to 150 mg/m² of doxorubicin. The ESMO guidelines advise performing an echocardiographic examination at the beginning of therapy and afterwards - three, six, nine, twelve, and eighteen months after its initiation. What is more, the specification

of troponin concentration in blood serum is recommended after each chemotherapy cycle (2).

When it comes to human-specific medicine, studies have shown that persistently high troponin I levels within 72h after medication administration are associated with the increased risk of cardiovascular events occurring, especially due to left ventricular systolic dysfunction that may happen in the future (3). Furthermore, patients who have not had a transient increase in cTnI levels identified have been at the reduced risk of developing cardiotoxicity-specific symptoms. It has been concluded that it is a useful tool when it comes to designing a circulatory monitoring regimen for each patient individually (3). The only limitation in said case is the fact that the increase in cTnI levels in blood serum due to anthracycline administration

is insignificant and requires more sensitive tests than the majority of methods currently commercially available in labs. It is also vital to assess the absolute value of said parameter. The information that it is below the threshold for upper reference standards adopted by the laboratory performing the test may in many cases not be sufficient.

In the study of anthracycline cardiotoxicity in dogs, Hallman et al. (2019) considered it justified to perform an ECG examination before the first, fourth, and sixth administration of doxorubicin, as well as to carry out rhythm assessment before each subsequent dose in patients being at risk of developing DCM, so predominantly, in representatives of the following breeds: American Cocker Spaniel, Boxer, Great Dane, Irish Wolfhound, Doberman Pinscher, and Newfoundland (4).

Table 1. Proposed intervals for monitoring the circulatory system in patients undergoing anticancer therapy. Own adaptation for veterinary medicine-specific purposes, basing on guidelines used in human oncology (5).

Baseline LVEF >50%	Baseline LVEF <50%	Radiotherapy with radiation field covering the heart
Test at the dose of 90 - 120 mg/m ²	Do not administer cytostatic medications with cardiotoxic potential when LVEF <30%	High cumulative doses >15 Gy or high single doses >1 Gy/day
Reassessment at the cumulative dose of 150 mg/m ²	Repeatable measurements before each administration	Co-occurring heart disease
Testing with each subsequent administration exceeding 150 mg/m ²	Discontinue therapy if LVEF declines ≥10% from baseline or ≤30%	Concurrent chemotherapy with anthracyclines
Discontinuation of therapy if LVEF decreases ≥10% from baseline and ≤50%		High-risk patient in terms of cardiovascular events: DCM, diabetes, obesity, hypertension

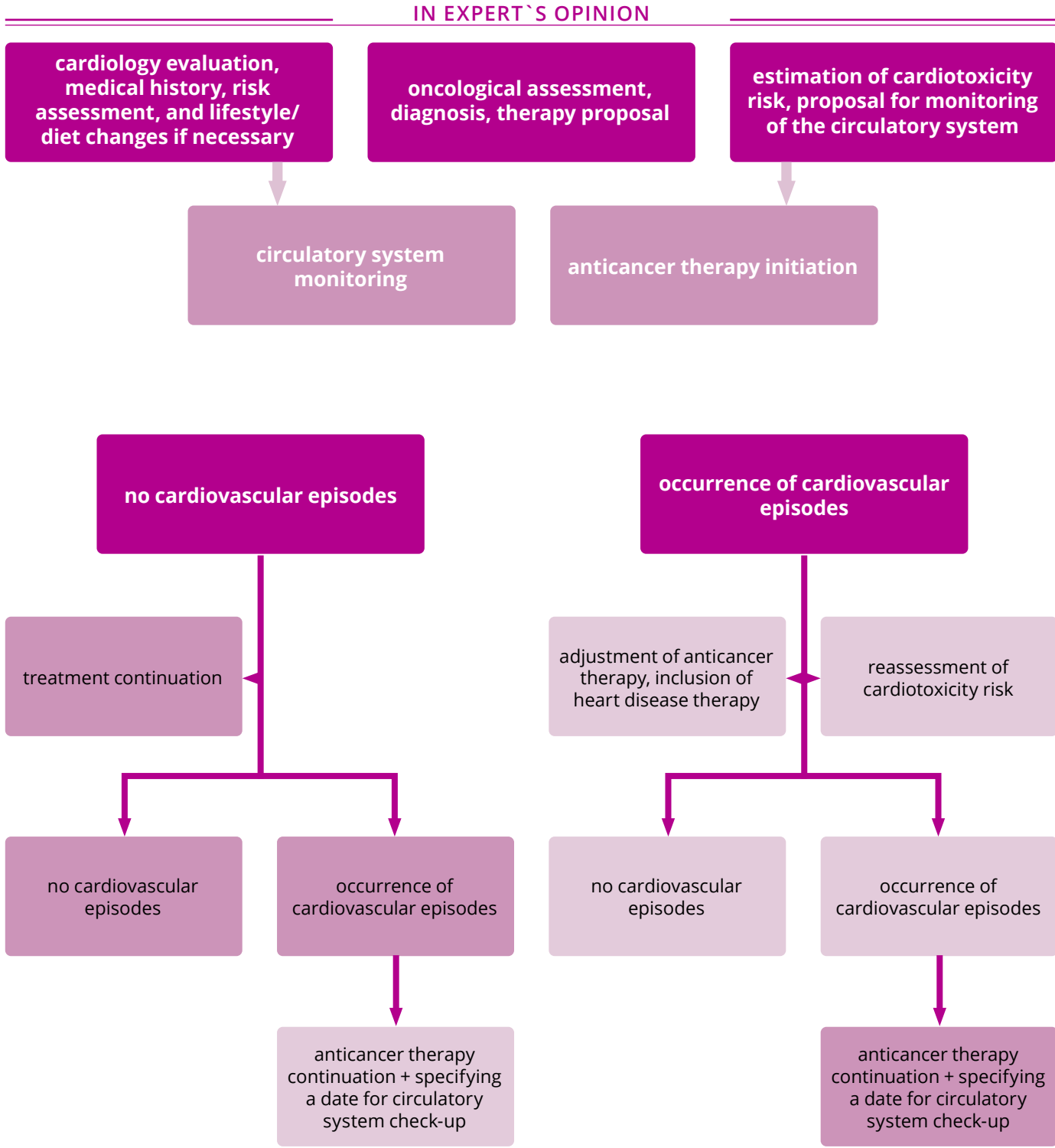


Fig. 1. Algorithm for monitoring cardiotoxicity in human medicine.

A properly developed monitoring regimen is extremely important for one specific reason. It has to be pointed out that there is a time window of about six months, during which the introduction of pharmacotherapy gives patients a remarkable chance to regain contractile function. What is more, in many scenarios, changes developing in the heart muscle may be reversible (6). After said time, the likelihood of contractile function returning to its original state decreases significantly.

Most serious cardiovascular incidents resulting from the use of anthracyclines or

targeted therapy in patients occur within the initial two years from the moment of therapy completion (7). In the context of such observations, the argument pertaining to potential cardiovascular issues developing after many years or even decades, especially in young adults treated in childhood (for leukemia for example), becomes less significant and valid.

Even though left ventricular diastolic dysfunction may reflect subclinical damage secondary to cytostatic medications use, no prognostic value of said parameter has been found. Due to said fact, its significance

remains uncertain (1). Relying exclusively on myocardial damage-specific serum biomarkers as a factor limiting cytostatic medication-based therapy turns out to be insufficient as well. It has not yet been clearly specified when troponin and nt-proBNP levels should be measured in patients undergoing chemotherapy. Nevertheless, it is widely known that a chronic increase in troponin I level above normal value indicates more serious cardiac damage caused by chemotherapy than transient increase (3). It has also not been specified what relationship NT-proBNP may have with



Table 2. Strategies allowing to reduce the risk of myocardial damage following anthracycline administration (9).

Strategy	Protective mechanism	Clinical benefit	Limitations
Free infusion	Reduction of C _{max}	Reduction of cardiomyocyte exposure to high concentrations of anthracyclines	Extended hospitalization time (in human oncology - even up to 48–72h)
Liposomal doxorubicin	Limited diffusion across the endothelium in the cardiac region	Preservation of antitumor activity with limited myocardial damage	Limited indications High cost
Dexrazoxane	Chelation of iron ions and mitigation of reactive oxygen species-induced damage + inhibition of IIβ topoisomerase (10)	Direct reduction of cardiotoxicity due to interacting with the pathophysiology of its development	Risk of side effects; Limitation of antitumor activity of anthracyclines (11); Safety in cats not specified (12)

left ventricular dysfunction in the context of chemotherapy-induced cardiomyopathy risk assessment. Monitoring methods may additionally depend on the type of medications administered to a specific patient. For example, when it comes to palliative therapy with tyrosine kinase inhibitors, patients are likely to require properly adjusted ECG monitoring, periodic blood pressure measurements, as well as ionogram-based assessments (8). It should also be remembered that to achieve most optimal result possible, the same diagnostic method should be used to monitor the circulatory system before, during, as well and after chemotherapy. Thanks to said approach, the obtained results may be easily compared.

Cardioprotection

The most valid strategy when it comes to preventing anthracycline cardiotoxicity is to limit the cumulative dose of medication administered within the scope of the therapeutic regimen of a specific patient to the necessary minimum. Nevertheless, it may not always be sufficient or even considered due to the importance of effective treatment of the underlying disease (cancer).

One may, however, identify many other methods of limiting damaging effects of cytostatic medications on the circulatory system, but they to a great extent depend on the type of medication opted for and the patient's condition. The continuous intravenous infusion of DOX extended in timeframe ranging from 30 to 60 minutes allows for a significant reduction in the maximum concentration of the medication in question (C_{max}) in blood serum, without at the same time affecting its antitumor efficacy (13). As far as human medicine is concerned, DOX analogues characterized by lower circulatory system damaging are also often taken advantage of (13,14) (15). As of currently, such a solution has allowed to reduce cardiotoxicity in the case of paclitaxel

as well (16), (17). Histopathological changes in the form of vacuolization and the loss of contractile fibers of canine cardiomyocytes resulting from the use of classical DOX have not been identified when liposomal forms have been opted for (18,19). The change in the medication formulation has also allowed to notably reduce other adverse effects, such as anorexia, weight loss, hair loss, as well as gastrointestinal symptoms (19).

According to recommendations that are typical for human oncology, the utilization of dexrazoxane is recommended only in women with breast cancer who have cumulatively taken more than 300 mg/m² of DOX. It should not be used in the ad hoc manner in every patient due to possible side effects, as well as because of reports of its antagonistic effect on the anticancer action of cytostatic medications (13). Despite the small research group, Pino et al. (2021) showcased that carvedilol administered at the dose of 0.39 mg/kg ± 0.04 twice daily reduces the deterioration of diastolic function due to the effect of DOX. Therefore, it has been concluded that it may have a protective effect on the circulatory system (20). When it comes to human oncology, the prophylactic use of angiotensin-converting enzyme inhibitors, β-blockers, angiotensin receptor antagonists, or sartans (ARBs) in the prevention of post-anthracycline cardiomyopathy remains controversial. Nowadays, it is recommended to opt for longer time intervals between the administration of two cytostatic medications with damaging potential, DOX and trastuzumab (2). In some cases, trivial approaches may be helpful, such as the supplementation of micro- and macroelements in cases of their deficiencies, which is especially true when it comes to potassium and magnesium (8).

Taurine constitutes more than half of amino acids in proteins building the heart muscle. Chemotherapy has a potential to significantly reduce its absolute mass. Thanks to its antioxidant, anti-inflammatory,

and anti-apoptotic effects, taurine supplementation in patients undergoing chemotherapy has allowed for a significant reduction in the loss of striated muscle mass building the myocardium. Nevertheless, additional studies are necessary in said field. What is more, there are currently no clear recommendations for the preventive introduction of taurine supplementation in patients taking cytostatic medications (21).

Brito et al. (2016) came to truly intriguing conclusions. The researchers proved that physical exercise in female rats subjected to chemotherapy during pregnancy had a protective effect on fetal cardiomyocytes, increasing their viability and limiting the cytotoxic effect of DOX by means of intensifying the antioxidant response, as well as ensuring protection protecting against DNA helix breaks (22).

Prevention in the preclinical phase

As of currently, numerous in vitro studies or examinations basing on experimental animals focus on finding substances that can inhibit damaging effects of cytostatic medications on cardiomyocytes. Since most of mechanisms of chemotherapy cardiotoxicity are based on inducing the increased production of reactive oxygen forms, oxidation of intracellular compounds, or pro-inflammatory action, compounds with an opposing effect may turn out to be useful in removing free radicals, increasing antioxidant enzyme response, or reducing pro-inflammatory cytokines generated in the body. Said properties have been identified in the case of bosentan (which is capable of preventing damage resulting from the administration of 5-FU) (23), simvastatin (24), silymarin (25), resveratrol (26), bee propolis (27), and natural flavonoids (28). Especially in the last group mentioned, numerous active substances have been discovered that have a beneficial effect on the circulatory system without the risk of causing serious adverse effects.

Ingredients

0.5 cup of powdered turmeric

2 cups of warm water

1.5 teaspoons of freshly ground black pepper

70 ml of coconut oil or cold pressed olive oil

Preparation

Mix all ingredients into a smooth paste. Administer twice daily with food.

Dosage: ¼ teaspoon to ½ teaspoon for smaller dogs, up to 1 teaspoon for large breeds. The paste can be stored in the refrigerator for up to 2 weeks.

Fig. 2. Recipe for a homemade cardioprotectant - a dietary supplement including both turmeric and black pepper.

In humans, canines, and rats, DOX increases serum levels of proinflammatory cytokines – interferon γ (IFN- γ), interleukin 1 β (IL-1 β), as well as tumor necrosis factor α (TNF- α). It also induces redox imbalance by increasing oxidative stress in cardiomyocytes, which is normally neutralized by glutathione peroxidase (GDH), catalase (CAT), and superoxide dismutase (D). Furthermore, blood tests show a notable increase in the concentration of myocardial damage biomarkers, including troponin I, creatine kinase (CK), lactate dehydrogenase (LDH), as well as aspartate aminotransferase (AST). Citrus-based bioflavonoid called hesperidin has remarkable bioactive properties, including antiapoptotic effect. It has showcased it when administered to rats receiving DOX at the dose of 100 mg/kg of body weight daily, 5 days a week. It has provided a significant cardioprotection (29), similarly to naringin (30), yet another citrus-based flavonoid, as well as indole-3-carbinol (I3C) that can be found in Brassicaceae plants (31). A carotenoid group-based compound, crocin, found in crocuses and gardenias, has showcased cardioprotection (assessed, among others, on the basis of reduced concentrations of cardiomyocyte damage biomarkers while compared to the control group), as well as demonstrated effectiveness in improving the serum lipid profile of the tested rats (32). A plant extract from *Kalanchoe integra* has effectively inhibited the production of nitric oxide, increased biochemical parameters related to cardiotoxicity (AST, ALT, ALKP, CK, and LDH), as well as stimulated the activation of

physiological defense mechanisms against oxidative damage, SOD, CAT, and GPX (33). Aside from biochemical effects, a significant reduction in histopathological changes of heart muscle exposed to the cardiotoxic effect of DOX has been observed as well (33).

The protective effect of flavone called cardamonin, obtained from *Alpinia purpurea*, has been confirmed in a mouse model basing on its antioxidant, antiapoptotic, and inflammatory response-inhibiting activity (34). Curcumin contained in turmeric has been shown to inhibit the destructive effect of DOX. To elaborate, it has improved heart rate, ECG recording (especially in terms of ST segment stabilization), CK and LDH profile in blood serum, as well as – similarly to plant extracts tested on rats – to a great extent eliminated pathological changes visible in the microscopic image. The potential mechanism underlying the cardioprotective properties of curcumin may be based on its basic antioxidant function. Nevertheless, researchers have also discovered a high potential of the compound in question to improve mitochondrial function (35). Curcumin protects not only against anthracycline cardiotoxicity, but also against topoisomerase I inhibitor, namely irinotecan (CPT-11) (36). Interestingly enough, for many years, veterinary medicine has had a “recipe” for an optimal dietary supplement to be given to chronically ill, geriatric, or cancer patients (Fig. 1). Coenzyme Q10 that is well-known in medicine and cosmetology has allowed for limiting the apoptosis of cardiomyocytes in mice with heart failure, reducing the concentration of myocardial damage markers and the undesirable effects of oxidative stress in a mouse model after the administration of DOX (37).

Ancient Chinese medicine has also provided a myriad of interesting answers. Oxymatrine obtained from *Sophora flavescens*, a plant commonly called Ku Shen that has been used in Eastern herbal medicine since the second century BC, has turned out to be a promising cardioprotectant in the context of combatting DOX side effects. Oxymatrine inhibits apoptosis and reduces oxidative stress in cardiomyocytes, which has been confirmed by in vitro studies on the rat H9c2 cell line, as well as directly, in vivo on rats (38).

New solutions for the protection against damaging effects of cisplatin on the heart are still being found. Most studies are conducted on small lab animals, in the case of which the protective effect of c-Met inhibitors (such as capmatinib) (39), venlafaxine (40), semaglutide (41), and sacubitril with valsartan (42) have been found. Some of the compounds studied have also allowed for increasing the anticancer potential of classical chemotherapy (39). Nevertheless, the main goal is to identify cardioprotectants that exert a protective

effect on cardiomyocytes in patients treated with cardiotoxic cytostatic medications. For example, ginger, which is widely known for its antioxidant, antiapoptotic, and anti-inflammatory properties, has shown a strong protective effect in a study on rats, largely eliminating the cardiotoxic potential of cisplatin (43). Similarly, curcumin, mentioned earlier as a potential protective agent against anthracycline damage, has shown remarkable effects in the case of cardiomyocyte damage induced by platinum compounds (44). One of polyphenols used as a part of natural therapies, namely - sinapic acid, or sinapic acid, being a derivative of coumaric acid found in mustard and olives, has allowed for the improvement of electrocardiographic parameters (duration of QRS complexes, QT interval), decrease in the concentration of proinflammatory cytokines, and a notable improvement of the antioxidant profile in a rat model (45). Cisplatin leads to the prolongation of QRS complex duration and QT interval, as well as to the increase in the concentration of TNF-α and IL-6. Furthermore, changes in the microscopic image of rat hearts exposed to cisplatin have been also significantly less advanced in the group of animals supplemented with sinapic acid (45). A rat model has shown that a natural component of citrus fruits and green vegetables, colloquially called vitamin P2, namely – hesperidin, can be an excellent dietary supplement reducing cardiotoxic effects of cisplatin. (46).

Even though the majority of examinations evaluating the efficacy of the aforementioned compounds as cardioprotectants have been based on mouse or rat models, it is possible that in the near future, they will be extended to clinical oncology of humans and pets, especially since said compounds are not toxic. What is more, in most cases, they are easily available and inexpensive. There are virtually no contraindications, apart from few exceptions related to specific individuals such as allergies, food intolerances, or taste preferences, to the introduction of supplementation based on the utilization of natural plant extracts.

Treatment

Systolic dysfunction

When it comes to human medicine, complications of anthracycline therapy having the form of systolic dysfunction are treated with angiotensin-converting enzyme inhibitors (ACEI), aldosterone antagonists (ARBs), or medications belonging to the β-blocker group (47). Patients having clinical symptoms of systolic dysfunction with LVEF% <40 are transferred to heart failure therapy alone, which is connected with the suspension of oncological treatment. In patients with LVEF% between 40 and 50%, control tests every 3 weeks are recommended (2). Similarly, in patients with



normal ejection fraction, chemotherapy can be continued, but caution and frequent echocardiographic checks are necessary. In asymptomatic patients with LVEF% <40 or a ≥15% drop from the baseline value below 50%, anthracyclines should stop being administered and pharmacotherapy for heart failure should be started simultaneously. Afterwards, the assessment of benefits in relation to risks is required for each patient individually (2).

Arterial hypertension

Patients taking VEGF inhibitors are particularly susceptible to hypertension secondary to anticancer therapy (48). When it comes to veterinary oncology, there are no pure inhibitors of said factor. Nevertheless, toceranib shows some activity in this area, apart from standard inhibition of receptor tyrosine kinases (49,50). Therefore, a necessary element of circulatory system monitoring in dogs and cats taking toceranib should be systematic blood pressure control.

It should be taken into account that oncology patients often take other groups of medications characterized by known prohypertensive effects, such as corticosteroids or nonsteroidal anti-inflammatory medications listed in the “ACVIM consensus statement: Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats” (51). Furthermore, hypertension has been identified in said group slightly more often than in the standard population of dogs. Therefore,

the aforementioned parameter should be kept in mind in the case of oncology patients (50). Corticosteroids have also been associated with an increased risk of AF in such patients.

According to human medicine guidelines, antihypertensive medications recommended for hypertension induced by tyrosine kinase inhibitors/VEGF inhibitors are, similarly to systolic dysfunction, ACEI, ARBs, as well as medications belonging to the group of β-blockers characterized by vasodilatory effect: carvedilol and nebivolol. Non-dihydropyridine calcium channel blockers (such as verapamil and diltiazem) are not recommended, predominantly due to their ability to inhibit cytochrome P450, which may result in unfavorable pharmacological interactions. On the other hand, dihydropyridine calcium channel blockers, such as amlodipine, may be taken advantage of successfully (47). Due to the lack of examinations on the treatment of chemotherapy-induced hypertension in canines and felines, the ACVIM recommendations should be followed, similarly to the treatment of standard arterial hypertension. The dose of the medication may be reduced or, in cases refractory to pharmacological treatment, the therapy should be discontinued, unless such an approach is associated with a significant harm done to the patient in terms of the underlying disease (51).

While selecting proper blood pressure lowering medications, the condition of the excretory system should be taken into account, as well as the need for weekly

blood pressure monitoring at the beginning of therapy in order to appropriately adjust the dose and type of medications. Later on, check-up can be done every 3 weeks (52).

Coronary heart disease

In the majority of cases, said health concern is associated with the administration of 5-FU, which may cause coronary artery spasms, endothelial damage, as well as myocardial ischemia (53). While opting for 5-FU, it is recommended to monitor the circulatory system, assess troponins, and provide prophylaxis in the form of nitrates or calcium channel blockers (52).

Arrhythmias

In oncological patients, there may be many causes of arrhythmia, ranging from extensive surgical procedures, chronic inflammations, or imbalances of the autonomic nervous system, through the manifestation of paraneoplastic syndromes (macro- and microelement disorders, acid-base and water-electrolyte balance disorders) and metabolic disorders, up to the heart muscle being attacked by a neoplastic disease. Arrhythmias may also occur as a side effect of anticancer therapy. Atrial fibrillation (AF) is the most common disorder diagnosed in patients. Fortunately enough, the occurrence of AF rarely requires physicians to interrupt or discontinue oncological therapy (47,52).

While assessing the etiology of observed arrhythmias, it is essential to assess electrolyte balance, exclude

Table 3. Medication doses in the treatment of chemotherapy-induced cardiac complications in pets.

Disorder type	Active substance	Dose	Notes
Systolic dysfunction (56)	Pimobendan	0.25 – 0.3 mg/kg bw PO Every 12 hours	Not used in human medicine
Arterial hypertension (51)	Benazepril, enalapril (ACEI)	0.5 mg/kg every 12-24h in dogs, every 12 hours in cats (benazepril), every 24h in cats (enalapril)	-
	Telmisartan (ARBs)	1 mg/kg every 24 hours orally	There have been reports of opting for 5 mg/kg body weight in dogs.
	Amlodipine (CCB)	0.1-0.25 mg/kg every 24 hours max 0.5 mg/kg, in cats also 0.625 – 1.25 mg per cat every 24 hours	Warning – double dosage in cats recommended!
	Propranolol (β-blocker)	0.2-1.0 mg/kg every 8 hours in dogs; titrate to achieve the desired effect; 2.5-5 mg/cat every 8 hours	To be used while treating rhythm disorders as well
	Atenolol (β-blocker)	0.25-1.0 mg/kg every 12 h in dogs, 6.25 – 12.5 mg/cat every 12 h	
Rhythm disturbances (57)	Digoxin	2.5-7 µg/kg every 12h PO in dogs; max 0.25 mg/dog PO every 12h; in cats 10 µg/kg PO every 24 – 48 h	Always titrate basing on effect and serum concentration
	Verapamil, diltiazem	Not recommended for oncology patients due to cytochrome P450 inhibition – possible pharmacological interactions	



Table 4. Examples of medications with known potential to prolong the QT interval and other risk factors associated with the development of TdP.

Medication category	Examples of active substances	Other factors
Antibacterial	Amantadine, clarithromycin, erythromycin, moxifloxacin, sulfamethoxazole with trimethoprim	Mature age, genetic predisposition in the form of polymorphism of genes encoding ion channels or liver enzymes metabolizing xenobiotics
Anti-cancer	Tamoxifen	Bradycardia
Antiarrhythmic	Sotalol, procainamide, amiodarone, flecainide	Hypokalemia
Prokinetic medications	Cisapride	Hypomagnesemia
Hormones	Fludrocortisone, vasopressin	CHF with low ejection fraction
Antidepressants	Amitriptyline, clomipramine	Rhythm disturbances
Antipsychotic	Chlorpromazine, haloperidol, methadone	Medication-specific interactions (ion channel blockers, cytochrome P450 enzyme inhibitors)

sepsis, as well as make sure that there is no thyroid dysfunction. If any of the aforementioned factors occur, it must be corrected before initiating antiarrhythmic therapy. β calcium channel blockers or non-dihydropyridine blockers (CCB) are recommended for rhythm control, whereas digoxin is more preferred in patients with impaired systolic function (47). AF increases the risk of embolic episodes. Therefore, it is recommended to introduce anticoagulant therapy in the form of low-molecular-weight heparin or rivaroxaban (47,54). Warfarin is not recommended due to its numerous interactions with other medications that may be administered. It should be remembered that in the case of thrombocytopenia (in humans <30,000/µL, in dogs and cats <40,000/µL) and/or coagulopathy, dual antiplatelet therapy is contraindicated.

Treatment based on TKI should be discontinued if severe arrhythmias occur in the form of long QT (47,52). As in the case of AF, the principle of correction of concomitant diseases that may lead to or exacerbate conduction disorders (electrolyte imbalance, destabilization of thyroid function, severe systemic infection) applies as well. Furthermore, the influence of other medications administered concurrently should be excluded, as QT prolongation may occur after the administration of antiemetics, as well as some antibiotics and antidepressants (47,52). Therefore, one of the most frequently used antiemetic medications in oncological practice is ondansetron, belonging to the group of 5-HT3 inhibitors. QT prolongation is dose-dependent, so in geriatric patients at high risk of multidrug interactions due to the treatment of other concomitant diseases, the recommended dose of the medication should be strictly adhered to (55). In extreme cases, QT prolongation can lead to life-threatening ventricular tachycardia, including sudden cardiac death.

Even though the therapy of circulatory failure resulting from an adverse effect of anticancer therapy does not differ significantly from the one pertaining to other etiological factors, it is important

to keep in mind certain aspects that may make it difficult to stabilize an oncological patient. Cancer patients may experience episodes of hypotension, be to a greater extent burdened with the likelihood of renal failure occurrence, as well as may react negatively to certain medication combinations (58). Scientists have been searching for new active substances that can restore contractile function and normalize the concentration of biomarkers associated with cardiomyocyte damage in patients suffering for circulatory failure, for example by opting for compounds affecting energy metabolism disorders in mitochondria (59) to ensure that cardiotoxicity associated with cytostatic drugs can be effectively treated.

Future of veterinary cardio-oncology

Even though LVEF% is considered by experts in the field to be one of the most important parameters when it comes to

assessing myocardial damage in patients undergoing chemotherapy, its reduction occurs when significant destructive changes affecting a large part of the myocardium are already present and the proper time window for the introduction of early pharmacological prophylaxis or supportive therapy has long been gone (6). Furthermore, GLS, which is even more sensitive with regard to detecting subclinical forms of cardiotoxicity, is influenced by external factors such as age, gender, and filling pressure. It has to be noted as well that it has been assessed only in patients with breast cancer or malignant hematological tumors treated with anthracyclines. Extrapolating the results of the discussed studies to the entire oncological pharmacotherapy would be a notable mistake, as there is the requirement to conduct detailed studies, especially on patients suffering from other cancer types or treated with other active substances with known cardiotoxic

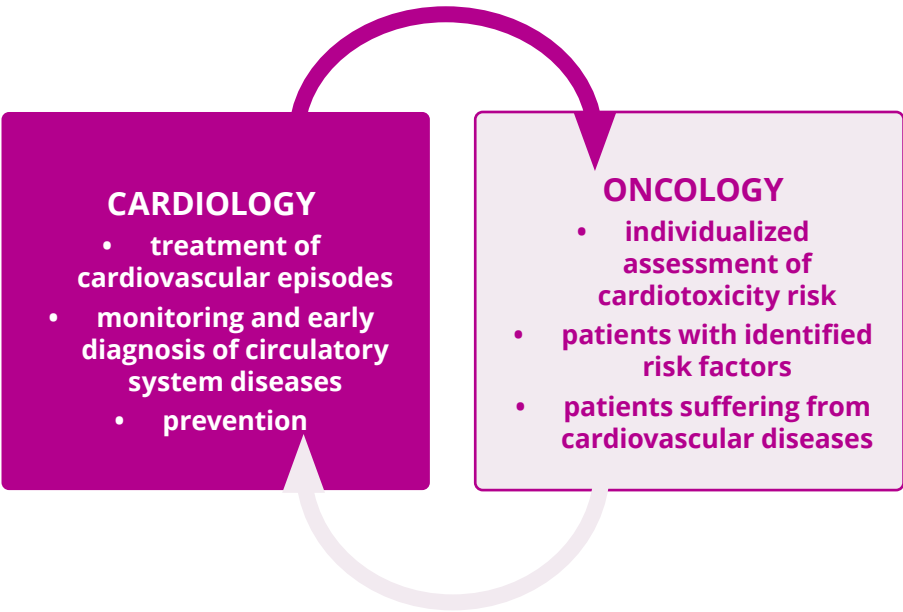


Fig. 3. Key tasks of teams operating in accordance with a holistic approach to cardio-oncology patients.



potential, such as cyclophosphamide or cisplatin. Even though cardiac-oriented magnetic resonance imaging is considered the gold standard for assessing changes in the circulatory system caused by oncological therapy, it is a highly expensive method that requires general anesthesia and cannot be used in patients with artificial pacemakers, with the overall number of such devices in veterinary medicine constantly increasing.

It has to be kept in mind that age, gender, as well as the condition of the excretory system may affect the concentration of atrial natriuretic peptides in blood serum. Currently available methods for troponin assessment may not be sensitive enough to detect subtle increases in their concentrations, especially when it comes to the serum of patients experiencing myocardial damage due to taking cytostatic medications or radiotherapy (60,61). The biomarkers of the future when it comes to cardio-oncology are microRNA and ceramides. It is currently known that MiR-1 is more effective than troponins with regard to predicting myocardial damage in patients with breast cancer taking anthracyclines (62). The early accumulation of ceramides inside rat cardiomyocytes after the exposure to doxorubicin precedes their apoptosis, which in turn allows to treat said parameter as an ideal biomarker for detecting myocardial damage at a very early stage (63). As a result of early detection of changes, biomarkers may prove to be useful in deciding whether to introduce cardioprotection, for example in the form of angiotensin-converting enzyme inhibitors, or – in extreme cases – to discontinue the use of a specific cytostatic medication (64).

Progress in molecular research with regard to genetic diseases in pets may, in the future, allow to identify gene variants responsible for sensitivity or resistance to myocardial damage induced by cytostatic medications.

As of currently, there are no universal guidelines regarding the frequency of cardiology check-ups in oncology patients, nor are there clear guidelines pertaining to the appropriate time or factors determining the need for cardioprotective therapy. What is more, there is a concern that the percentage of patients experiencing cardiotoxicity is still underestimated due to its asymptomatic course and imperfect diagnoses. Yet another factor that makes it difficult to transfer recommendations for oncology patients from those taking advantage of classic heart failure treatment is the fact that most studies on CHF have excluded patients with cancer from the study group. It is known that cancer and circulatory system diseases have common risk factors, which include hypertension, diabetes, obesity, and exposure to cigarette smoke. Due to the close relationship and common coexistence of humans, canines,

and felines, the same living environment and exposure to similar xenobiotics in everyday life indicate that exactly the same complications and risk factors can be expected in pets.

Summary

Considering remarkable gaps in knowledge pertaining to the nature of chemotherapy-induced cardiotoxicity in pets, it is rather problematic to establish specific guidelines that are ready for use in clinical practice. Nevertheless, anthracycline cardiotoxicity may have a significant impact on forecasts of oncological patients, whose survival time is estimated at more than six months (4). Taking into account rapid progress in oncology, both veterinary and human one, it is worth considering whether in five years, effective and long-term anticancer therapy will be available for pets, making cancer-related diseases to be treated similarly to other chronic diseases. Therefore, it will become necessary to develop methods of preventing, monitoring, and treating serious adverse effects on the circulatory system that are often associated with the risk of premature death of a patient suffering from cancer.

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Diet and supplements in cancer diseases in animals

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Abstract: Cancer is a chronic and devastating disease, the treatment of which requires the combination of pharmacotherapy, radiotherapy, oncological surgery, as well as diet therapy. General recommendations are oriented towards a high-fat, high-protein, low-carbohydrate diet. Omega-3 fatty acids, some amino acids, and antioxidant-based complexes are also advised in the course of anticancer therapy.

Keywords: diet, cancer, dog, cat

Cancer is a chronic and devastating disease, the treatment of which requires the combination of pharmacotherapy, radiotherapy, oncological surgery, as well as diet therapy. By means of combining the aforementioned forms of treatment, it is in some cases possible to achieve remission or at least notably improve the quality of life of an ill animal. Nevertheless, it is remarkably difficult to discuss unified dietary guidelines, as they are frequently dependent on the patient and have account for: current health condition, stage of the disease, animal condition, occurrence of comorbidities, and many others. The standard nutritional approach is oriented towards the introduction of a high-fat, high-protein diet characterized by low carbohydrate content and based on supplementation with compounds that can grant factual benefits to the animal treated (such as Omega-3 acids, antioxidant complexes, etc.).

Cancer cachexia

"Cancer" cachexia, or wasting, is typically defined as the loss of body mass (adipose tissue and lean muscle mass) resulting from the impact of excessively produced inflammatory mediators and hormones (including cytokines, catecholamines, cortisol, insulin, and glucagon). Such a state of affairs directly leads to the body to be unable to take advantage of energy from fat or produce it from amino acids, which causes muscle mass loss. Wasting is on many occasions accompanied by a growing lack of appetite, limited regeneration, and notable, rather severe immunity impairment. It leads to a drastic deterioration of the quality of life of a given animal, which may in turn directly translate into a shortened lifespan. Nevertheless, the outcomes of most recent studies point out that the entire process leading to wasting is very likely to begin much earlier, before the first clinical symptoms appear. It potentially offers great

opportunities when it comes to counteracting cachexia development (5).

Metabolic changes and their impact on diet balance specification

In the course of cancer, a myriad of metabolic changes take place, mainly concerning carbohydrates, which are the most efficient energy source for cancer cells. The utilization of simple sugars leads to the overproduction of lactates, which can be considered to be an additional metabolic 'burden' for the body. It has to be pointed out that their effective elimination requires additional energy expenditure. It has been proven in dogs with lymphoma that were given a diet based on a high content of easily digestible carbohydrates (17). At the same time, while reversing the approach opted for and introducing a low-carbohydrate, high-fat diet, a greater likelihood of remission was observed in ill animals. Therefore, when it comes to cancer, it is typically advised for the diet not to contain more than 20% EM from carbohydrates (25% carbohydrates in dry matter). At the same time, it is recommended to increase the share of fiber, especially in the case of gastrointestinal tract-related oncological diseases. Fiber, especially its fermentable fraction, allows for balancing the microbiota and producing short-chain fatty acids that are highly beneficial for the body of the patient.

The second dietary component most frequently utilized by cancer cells are proteins, which provide energy by being a part of the process of gluconeogenesis (16). The unavailability of amino acids and their derivatives limits cell repair and regeneration processes, reduces immunity, as well as hinders digestive processes. Furthermore, some amino acids may be preferentially used by the tumor. Nevertheless, most of them cause tumor growth limitation or

metastasis inhibition. Arginine can be provided as a fitting example, as it stimulates lymphocyte blastogenesis. When added to parenteral solutions, it inhibits the growth and metastasis of tumors in rodents (2,20). Glycine has been proven to have a strong effect when it comes to reducing cisplatin cytotoxicity. It also reduces methotrexate toxicity (7). When administered to rats at the dose of 1 g/kg of body weight for 11 weeks, it significantly reduced the glutathione concentration and increased the efficiency of cancer cell apoptosis process. Glutamine is still considered to be a rather controversial amino acid. It has a strong trophic impact on enterocytes, but can also be taken advantage of by cancer cells, as confirmed by studies on rats suffering from mammary gland tumors

Fat is the safest nutrient when it comes to oncological diets. Its use by cancer cells is very limited, which allows the body to preferentially use energy from it. Its content in the oncological diet should range from 50 to 65% of energy supplied from fat (25-40% fat in dry matter). Nevertheless, a high-fat diet is not always the optimal solution. It is contraindicated in hyperlipidemia and concomitant pancreatic diseases. Omega-3 acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are also of significant importance in diet-oriented therapy. Their content in oncological diets is advised to exceed 5% of dry matter, with the total fat content in the diet ranging from 25 to 40% of dry matter. The optimal ratio of Omega-6:Omega-3 acid has not yet been determined, but it is assumed that it should be close to 1:1. EPA and DHA acids inhibit tumor growth and metastasis. What is even more, they play a significant role in the process of normalization of lactate and insulin concentrations, inhibit protein degradation, as well as stimulate their synthesis. By reducing proinflammatory cytokine concentration, they are likely to stabilize appetite and inhibit cachexia progression (4). When it comes to dogs suffering from lymphoma, whose diet was supplemented with the combination of Omega-3 acids and arginine, survival time was prolonged (14). In the case of radiotherapy of skin cancers in dogs, a significant reduction in side effects associated with the radiation process was observed, as well as the acceleration of wound healing (1). Said acids, while com-

bined with various fiber types, are also used in the colon cancer treatment. Their effectiveness was confirmed in rats, in the course of treatment of which, the combination of fatty acids, pectin, and cellulose was opted for.

An oncological diet should be based on complete and balanced foodstuffs. Therefore, it is recommended to add all key vitamins and minerals necessary for animals to meals. Nevertheless, it is not advised to exceed the recommended amounts, as it is still not known to what extent they can be used by cancer cells. One should be very careful when administering them in excessive amounts, apart from confirmed cases of their remarkable efficiency. A fitting example is undoubtedly vitamin E, which acts as an antioxidant and protects genetic material from adverse effects of free radicals. However, it has to be pointed out that in a study on rats during which a mixture of fish oils and vitamin E was used, an antioxidant-specific protective effect was observed in relation to cancer. It was not only not expected but also undesirable. Currently, examinations are being carried out on the utilization of antioxidant potential of plant-derived compounds, such as gallate epigallocatechin (from green tea), genistein (from soy), curcumin (from turmeric), silibinin (from milk thistle), and quercetin (from onions and apples) (10). In the majority of cases, remarkable efficiency of the aforementioned active substances was observed in the course of in vitro examinations. For example, curcumin obtained from turmeric (*Curcuma longa*), which is characterized by anti-inflammatory, antioxidant, and anti-cancer effects, was tested in studies on canine osteosarcoma cancer cells, human melanoma, and breast cancer. Within the framework of said experiments, the reduced viability of cancer cells was observed when curcumin was present. A similar effect was identified in relation to leukemia, breast cancer, osteosarcoma, and hepatocellular carcinoma cell lines while opting for quercetin, a flavonoid present in numerous types of fruits and vegetables (such as red onion and grapes). Furthermore, quercetin has been shown to act as an inhibitor of metalloproteinases 2 and 9 (MMP-2, MMP-9) that may prevent cancer cell metastasis. By stimulating the synthesis of proapoptotic proteins (Bax, FasL) and reducing antiapoptotic protein synthesis (Bcl-2), it induces the process of programmed cancer cell death. Nevertheless, as it is in the case of previously discussed compounds, the efficiency of quercetin has still to be confirmed within the scope of in vivo examinations.

When it comes to cancer therapy, the nitrosation reaction inhibition effect is also taken advantage of, as it blocks the carcinogenesis process. Such effect has been found for vitamins E and C. Nevertheless, their effective doses are very high and range from

100 to 3200 IU per animal per day in the case of vitamin E and from 250 to 20,000 mg per animal when it comes to vitamin C (10, 11). Yet another effect pertaining to feline skin cancer cells (such as squamous cell carcinoma) has been demonstrated by natural and synthetic derivatives of vitamin A (retinol, retinal, and retinoic acid). They stimulate cancer cells to differentiate, which may increase their susceptibility to chemotherapy and radiotherapy. It has to be stated at this point that the recommended doses of vitamin A are high and amount to 20,000 IU to be administered within a week (10,19).

As far as cancer in humans and dogs is concerned, a decrease in plasma selenium concentration has been demonstrated. Furthermore, dogs suffering from lymphoma and osteosarcoma have also been shown to have decreased chromium and iron concentrations. Studies on rats have proved that introducing selenium into diet inhibited carcinogenesis processes in the colon, mammary glands, and in the stomach. In mice, selenium use reduced cisplatin nephrotoxicity, while at the same boosting its anticancer effect (15,10). It should be remembered, however that selenium has a very small usage-related safety margin and can easily be overdoled (22).

When it comes to cancer therapy, the synergistic anti-catechetic effect of the combination of HMB (3-hydroxy-3-methylbutyrate), arginine, and glutamine is also taken advantage of. It is believed that HMB can inhibit proteolytic enzyme activity in skeletal muscles and/or - through changes it undergoes in the body - stabilize muscle cell membranes (9). Said fact allows for muscle fiber strengthening, which become more strain-resistant. Additionally, muscle cell breakdown and exhaustion do not occur so quickly. Recommended doses for dogs range from 35 to 50 mg/kg bw/day.

To sum up, a proper diet, ensuring optimal nutrition, can prove to be a remarkable support of the oncological therapy opted for. Additional substances and supplements, while utilized sensibly and having scientifically proven effects, can improve the quality of life of an ill animal.

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Liquid biopsy – the future of diagnostics

Possibilities of using liquid biopsy and next-generation sequencing (NGS) with regard to oncological diagnostics and therapy monitoring in canines

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Abstract: It can be said without the shadow of a doubt that the development of veterinary medicine in recent years has been exceptionally dynamic. New diagnostics-related and therapeutic possibilities have been emerging. The majority of veterinarians consider the upcoming future to likely bring some hope. Will solutions allowing to correctly diagnose and cure all the patients be developed? It is not likely to happen soon, but it is still worth following most current breakthroughs and familiarizing oneself with innovative solutions that modern veterinary medicine offers.

Canine cancers

One of medical branches experiencing a spectacular evolution is veterinary oncology. It is undoubtedly a field in the case of which professional knowledge is inextricably linked with difficult decisions and emotions. It also has to be mentioned that the prevalence of various cancer types in animals is growing at a very fast pace.

Cancer is considered by experts to be one of leading causes of death in canines. It is estimated that 30% to 50% of dogs will develop cancer during their lifetime. Said risk is even greater in older animals. It means that every one in three dogs will be affected by cancer during its life. Cancer is diagnosed in about 8% of dogs each year, with its incidence being 10 times higher than in humans, as the risk of cancer is directly correlated with a notably shorter lifespan of the discussed animals.

Fortunately enough, the development of modern diagnostic technologies allows for more efficient detection and treatment of such diseases. According to carried out research, as many as 93% of veterinary oncologists declare readiness to take advantage of latest diagnostic methods that can significantly improve the effectiveness of cancer treatment in canines.

The incidence of cancer occurrence in dogs, similarly to humans, is influenced by genetic and environmental factors. One can identify mutations that increase the likelihood of certain cancer types developing in specific dog breeds. It is one of unintended side effects of selective breeding. Dogs living with humans are also exposed to numerous carcinogens.

Furthermore, canine cancers carry a significant risk of mortality, because many such issues are diagnosed in their advanced stages, when the cancer has already spread microscopically or macroscopically, making

it impossible for professionals to cure completely. A remarkably high incidence of said types of diseases in dogs makes oncological care the key element of animal-oriented health care.

Cancers perceived as genome-specific diseases

At the initial stage, cancers were defined by professionals primarily by identifying either the exact organ or tissue of their origin or by specifying cellular characteristics. Clinicians' capabilities of understanding and describing various cancer types were limited to macroscopic and/or microscopic examination. Developments in the field of molecular medicine done over the past two decades have revealed that normal cells accumulate random genomic changes over time as a result of DNA replication errors, as well as of exposure to endogenous factors (such as free radicals) and environmental (exogenous) carcinogens, including various forms of radiation and mutagenic chemicals that can be found in food and air.

A particular cancer develops when one or more of the aforementioned changes allow a cell population to grow in an uncontrollable manner. The vast majority of random changes occurring in cells are quickly repaired by intracellular DNA repair mechanisms. If they are severe enough and cannot be reversed, they lead to cell death without at the same time causing any adverse effects that would impact the organism as such. Nevertheless, when such random changes occur at specific locations in the genome and are not repaired, a chain of events is set in motion. It ultimately leads to the development of cancer, often in its malignant variant. The aforementioned changes stimulate the affected cells to grow and/or survive, either by increasing their replication or inhibiting the processes controlling their division.

After some time, tumor growth may be

further accelerated due to the accumulation of new changes occurring more or less regularly. Said state of affairs causes tumor cells to replicate even more rapidly, invade surrounding tissues, spread to distant organs via both lymphatic and vascular pathways, as well as evade immune system-specific mechanisms. When the cell count reaches about a billion, the tumor reaches the size of about 1 centimeter in diameter and weighs approximately 1 gram. At that stage, the mass becomes detectable by means of physical and imaging-oriented examinations. It may also start causing clinical symptoms such as bleeding, lameness, weight loss, or apathy to occur.

With the growth of malignant tumors, they develop the ability to invade adjacent areas and metastasize to distant body parts by accumulating DNA-specific changes in key genes.

The extreme heterogeneity of genomic features of various cancer types combined with the fundamental understanding of cancer as a "genome-specific disease" has allowed for novel diagnostic approaches reaching far beyond the concept of a specific test for a given cancer type. Such an approach favors the so-called "pan-cancer" model, in the case of which a single, comprehensive diagnostic test can be taken advantage of in order to properly detect and characterize multiple cancer types.

Liquid biopsy - a modern approach to cancer diagnostics

Traditional oncological diagnostics is considered to be a complicated and very often invasive process. It includes, among others, imaging examinations or tissue biopsies. Even though they are remarkably effective, they can be associated with certain complications. Liquid biopsy makes it possible to analyze tumor biomarkers identifiable in body fluids, such as blood, urine or cerebrospinal fluid. Said fluids can be obtained in a marginally invasive fashion.

Liquid biopsy-oriented analysis of cancer patient blood may cover tests being done for circulating nucleic acids (primarily cell-free DNA, which incorporates circulating tumor DNA), circulating tumor cell (CTC) proteins, as well as numerous other biomarkers.

The possibility of identifying various biomarkers in blood offers unique benefits to professionals, especially with regard to patients suffering from factual or suspected cancer, in the case of which obtaining a tissue sample to be used for the purpose of traditional histological analysis can prove to be exceptionally risky, troublesome, or in some scenarios – even impossible. The conventional road to diagnosing cancer in

the field of oncology diagnostics. Thanks to the introduction of next-generation sequencing (NGS) technologies in the 2000s, liquid biopsy became a vital tool for precise molecular profiling of various cancer types. The synergy of discussed technologies allows for rapid, noninvasive cancer detection and monitoring, which is vital not only in human-specific, but also - in veterinary medicine.

In the course of programmed cell death

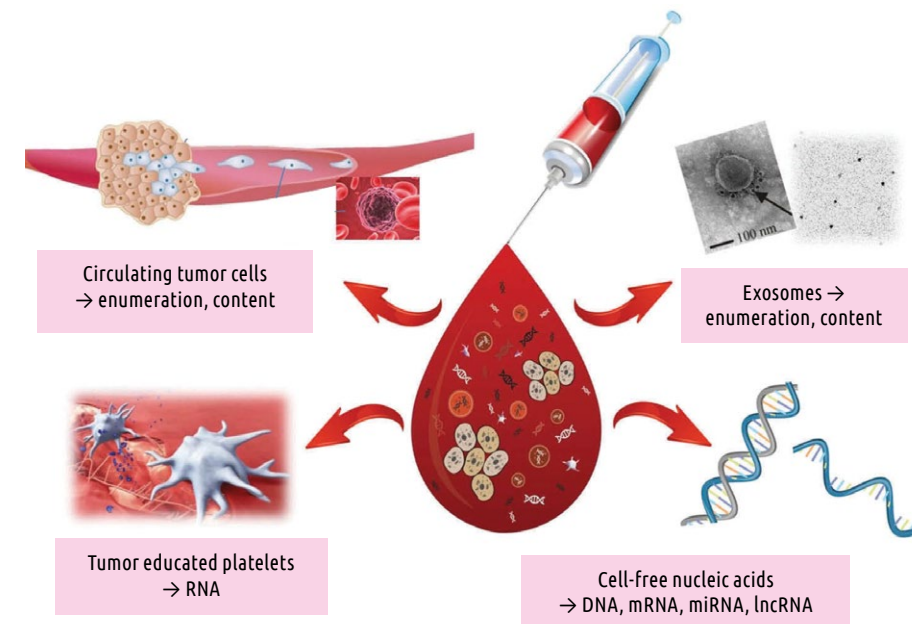


Fig. 1. Liquid biopsy provides clinically vital pieces information and blood samples can be analyzed from different angles.

Source: Emmy Boerrigter, Levi N. Groen, Nielka P. Van Erp, Gerald W. Verhaegh & Jack A. Schalken (2019): Clinical utility of emerging biomarkers in prostate cancer liquid biopsies, Expert Review of Molecular Diagnostics

companion animals varies depending on the characteristics of the patient, cancer type, as well as its location. When it comes to most commonly used diagnostic methods, one can identify cytology and biopsy, which allow for making either a preliminary or a definitive diagnosis, developing a treatment plan, as well as offering viable forecasts.

Clinical and economic challenges that are connected with tissue analysis have led experts to engage in the search for the so-called "non-invasive" approaches oriented towards the analysis of biomarkers identifiable in easily accessible body fluids, such as blood, urine, or various secretions. Out of all the available biomarkers, the analysis of cell-free DNA released from cancer cells seems to have the greatest potential.

cfDNA - specificity and origin

Liquid biopsy as such dates back to the 1940s, when free DNA (cfDNA) was for the very first time detected in blood. Nevertheless, it was not until the 1990s that cfDNA derived from cancer cells was identified. Said breakthrough offered new possibilities

(which is called apoptosis) and necrosis, both the cell and nuclear membranes disintegrate, releasing their contents into the bloodstream. Among such released components, there are DNA fragments, which – after leaving the cell and its nucleus – are referred to as "extracellular DNA" or cell-free DNA (cfDNA). cfDNA fragments rapidly undergo the process of degradation as a result of activation of metabolic processes. They are characterized by a very short half-life, ranging from 15 minutes to several hours in both humans and canines. They are typically removed from the body within a few days (168–170). The continuous turnover of body cells ensures a constant, stable amount of cfDNA in the bloodstream, allowing for its proper analysis by means of opting for advanced technologies, such as next-generation sequencing (NGS) for example.

In order for liquid biopsy to be clinically useful to the greatest extent possible, it has to grant professionals the chance to detect multiple classes of cancer-associated genomic alterations in cfDNA with a remarkable accuracy, even at low circulating concentrations. What is more, cfDNA biology allows for the assessment of

circulation-specific genomic features that may provide additional pieces of information pertaining to the presence and origin of a given cancer.

As of now, the only technology that can be utilized to simultaneously analyze all major classes of genomic alterations in cfDNA, as well as to examine features such as methylation and fragmentation patterns, is next-generation sequencing (NGS). Top liquid biopsy-based tests currently used or being under development in the field of human medicine take advantage of cutting-edge NGS techniques in order to assess a wide range of alterations and features in the genome that can be associated with cancer.

Liquid biopsy - clinical applications in oncology

Liquid biopsy offers professionals the desired synergy between the convenience typical for a blood sample and the efficiency characteristic for genomic technology. It is rather unlikely to completely replace traditional tissue biopsy when it comes to diagnosing and treating cancer in animals. Nevertheless, it has to be pointed out that while taking into consideration its noninvasive nature and the capability of detecting cancer signals coming from any malignant lesion in the body, it offers added value in a myriad of clinical scenarios.

Liquid biopsy can have multiple uses in veterinary medicine, such as:

- 1. Early cancer diagnosis:** Early stage cancer detection when clinical symptoms are not yet visible or when patients are considered cancer-free to perform screening tests.
- 2. Therapy customization:** Choice of targeted therapy based on the tumor mutational profile.
- 3. Treatment monitoring:** In the case of long-term treatment (chemotherapy, radiotherapy), liquid biopsy allows for monitoring the response of the patient to the treatment opted for, including resistance mutations emergence or new genomic variants occurring that can be potentially treated by opting for specific medications.
- 4. Recurrence detection:** Identification of minimal residual disease (MRD) occurring immediately after surgery. In patients in complete remission or after recovery, it allows for relapse detection and risk assessment.
- 5. Therapy personalization:** Targeted treatment selection basing on genetic profile.

Liquid biopsy - limitations and challenges

cfDNA analysis based on taking advantage of liquid biopsy has the potential to revolutionize certain aspects of veterinary oncology by allowing for safe, noninvasive testing at intervals tailored to the specificity of each patient and case. Nevertheless, one

has to remember that it will not solve all cancer-related problems in animals and that has important limitations that cannot be neglected.

One has to remember that some tumors may not release sufficient amounts of ctDNA into the bloodstream to allow for their detection and characterization by means of opting for liquid biopsy. It may be the case especially when it comes to smaller, poorly-developed tumors or tumors releasing limited amounts of ctDNA (as it is the case with central nervous system tumors).

While taking into account the novelty of liquid biopsy, extensive education-oriented undertakings will be required before its use can become widespread in veterinary. It is a practical limitation of both the rate and scope of adoption of the discussed technology.

Closing remarks

Thanks to the remarkable development of human oncology, numerous novel diagnostic and therapeutic opportunities have emerged in veterinary medicine as well. One of such solutions is undoubtedly liquid biopsy, which is a promising tool with the potential to revolutionize oncological patient treatment. When it comes to veterinary medicine, where invasive diagnostic methods can be risky or difficult, liquid biopsy may grant new possibilities with regard to cancer diagnosis and treatment in companion animals. While compared to currently utilized methods of monitoring treatment response, liquid

biopsy is a complementary tool that will certainly allow for a better understanding of tumor evolution and development.

As the new era of genomic medicine approaches, convenient and noninvasive tools, including liquid biopsy, will allow veterinarians to provide best care possible to cancer patients, predominantly by detecting tumors at an early stage, when they can be cured successfully. Said tools also allow to select targeted therapies, monitor treatment response, as well as detect relapse. Future developments in genomic technologies combined with integrations with other diagnostic tools may further increase the importance and usefulness of the method in question.

Modern tools, while being properly combined with technological developments in the field of DNA profiling, have been notably changing the approach to cancer diagnostics. The focus has been shifting towards early detection with the goal being to improve treatment outcomes. Liquid biopsy-based tests have already revolutionized cancer management in human medicine. They are now very likely to have a similar impact on veterinary medicine. Are we ready for such a revolution?

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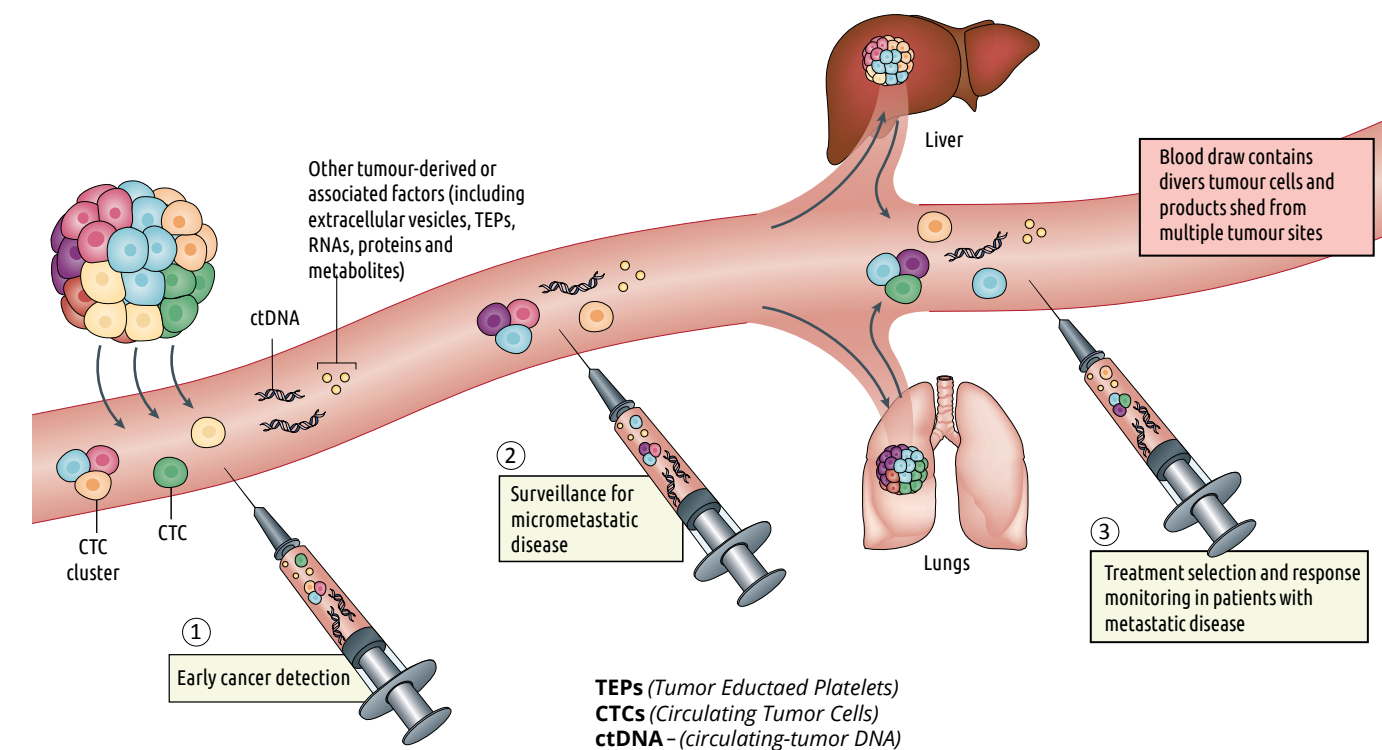


Fig. 2. Possible liquid biopsy application.

Source: Ignatiadis, M., Sledge, G.W. & Jeffrey, S.S. Liquid biopsy enters the clinic — implementation issues and future challenges. Nat Rev Clin Oncol 18, 297–312 (2021).

NEW

DIAGNOSTICS +

Vet Expert K9-LiquiDX Canine Cancer Check – an advanced diagnostic solution designed for oncology patients

A liquid biopsy-based test enables the detection of circulating tumor DNA (ctDNA) released into the bloodstream by dying cancer cells. The isolated genetic material undergoes Next-Generation Sequencing (NGS), and the obtained data is subjected to a detailed bioinformatics analysis.

HOW DOES THIS TEST BENEFIT YOU?



- ✓ **Minimally invasive procedure** – uses venous blood, eliminating the need for patient anesthesia.
- ✓ **Early cancer detection** – identifies minimal residual disease (MRD) before clinical symptoms appear.
- ✓ **Rapid intervention** – enables earlier treatment, leading to better outcomes, improved prognosis, and enhanced quality of life for patients.
- ✓ **Precise monitoring** – allows for the development of personalized treatment strategies based on an individual genetic profile.
- ✓ **Comprehensive test report** – provides access to detailed data on 69 possible mutations characteristic of various cancer types.

HOW TO USE VET EXPERT K9-LIQUIDX CANINE CHECK TEST?

- Step 1: Blood Draw:** Collect 5–9 ml of fresh venous blood from the patient into a special tube with a stabilizer. Important! The tube must be ordered in advance from a Vet Expert local distributor.
- Step 2: Mix Sample:** Gently invert the sample 10 times.
- Step 3: Shipping:** Properly secure the blood sample in the designated packaging, schedule a pickup (cc@vetexpert.pl), and send it to the reference laboratory. Important! You will receive the complete set of shipping documents via email.
- Step 4: Genetic Material Sequencing:** In a specialized laboratory, the sample undergoes advanced Next-Generation Sequencing (NGS).
- Step 5: Data Analysis:** Our team of experts analyzes the collected data and compiles it into a personalized test report, which is delivered via email within 14 days.



Visit our platform
watch the
webinar, and
learn about our
product.



NEW – Vet Expert K9-LiquiDX Canine Cancer Check.
What can a liquid biopsy do for your canine
oncology patients?



Presenter:
Maciej Parys DVM, PhD



RECOVERY DOG



Monoprotein, high protein and high fat dietetic feed with added Omega-3 acids from salmon oil, for dogs in convalescence

Composition:

Meat and derivatives (61% chicken); rice (6%); minerals (1%); oils and fats (0.2% salmon oil), MOS (0.1%), FOS (0.1%).

Analytical components:

Protein: 12%, Fat: 10.2%, Fiber: 0.2%, Ash: 2.2%, Moisture: 75%, Fatty acids: Omega-6 1.1%, Omega-3 fatty acids: 0.17%, ME: 138 kcal/100 g

Packaging:

400 g



INTESTINAL DOG



Monoprotein dietetic feed with an easily digestible source of protein (lamb) that balances digestive disorders and limits intestinal absorption disorders.

Composition:

meat and animal products meat and animal products (50% lamb), vegetables (10% potatoes), plant products (0.1% Yucca Schidigera, 0.1% FOS, 0.1% MOS) oils and fats (0.1% salmon oil).

Analytical components:

Protein: 8.6%, Fats: 5.2%, Ash: 1.9%, Moisture 8%, Calcium 0.18%, Phosphorus 0.15%, Potassium 0.30%, Sodium 0.16%

Packaging:

200 g i 400 g



RECOVERY CAT



Monoprotein, high-protein and high-fat dietetic feed for cats in convalescence.

Composition:

Meat and derivatives (68% chicken); cereals (2% oat flakes); minerals (1%); oils and fats (0.2% salmon oil), MOS (0.1%).

Analytical components:

Protein: 10.8%, Fat: 6.3%, Fiber: 0.4%, Ash: 2.7%, Moisture: 77%. ME: 114.3 kcal/100 g.

Packaging:

100 g



INTESTINAL CAT



Dietetic feed with easily digestible protein source: chicken, beef, balancing digestive disorders and limiting intestinal absorption disorders.

Composition:

meat and offal (50% chicken, 18% beef), vegetables (2% potatoes), minerals (1%), sugars (0.1% MOS; 0.1% FOS), oils and fats (0.2% salmon oil), yeast (0.1%).

Analytical components

Protein: 11.1%, Fat: 4.9%, Ash: 3%, Fiber: 0.4%, Moisture: 78%, Na: 0.22%, K: 0.24%, ME: 96.4 kcal/100g.

Packaging:

100 g

SUPPLEMENTS



NEUROSUPPORT



A preparation in twist-off capsules, intended for dogs and cats to support the optimal functioning of the nervous system. Contains a complex of ingredients with strong antioxidant properties.

Composition:

fish oil (source of EPA and DHA acids), dried acerola (*Malpighia glabra* L.), dried flowers of marigold (*Tagetes erecta* L.) (source of lutein and zeaxanthin), lecithin, vitamins, minerals and plant extracts, including: extracts from the skin of the grapevine (*Vitis vinifera* L.), from green tea (*Camellia sinensis* L.) and from dried rhizomes of turmeric (*Curcuma longa* L.).

Packaging:

45 caps.

BIOPROTECT ULTRA



A preparation intended for dogs and cats, helping to restore the balance of the intestinal microbiome and the proper functioning of the intestinal barrier in the case of gastrointestinal dysbiosis. Recommended for long-term use as a support in conditions of improper functioning of the digestive tract, in particular the pancreas and enteropathy of various origins.

Composition:

Yarrowia lypolitica, galactooligosaccharides, inactivated *Limosilactobacillus reuteri*, microencapsulated sodium butyrate, magnesium stearate.

Packaging:

30 caps.

Additives per capsule zootechnical:

Lactobacillus acidophilus 5 0 m g (5 x 10⁹ CFU), *Enterococcus faecium* 5 mg (5 x 10⁸ CFU) and dietetic: L-tryptophan 50 mg.

CARDIOVET



Tablet preparation, intended for dogs to support the heart and proper functioning of the circulatory system.

Composition:

magnesium stearate, selenium yeast.

Packaging:

90 caps.

Dietary additives (g/kg):

L-carnitine L-tartrate 428.6 g, taurine 158.7 g, vitamin E 47600 IU.



NEW

COSMETICS

COMPREHENSIVE LINE OF DENTAL PRODUCTS

Veterinary Oral Care

CARYODENT®



CARYODENT® ENZYMATIC TOOTHPASTE:



vol. 50 ml



CARYODENT® ENZYMATIC SPRAY:



vol. 50 ml



Enzymatic paste (a complex of natural enzymes), based on β-caryophyllene with the addition of hydroxyapatite, limits the growth of dental plaque, stabilizes the oral microbiome and supports the remineralization processes of tooth enamel

The adhesive spray with a quiet applicator has a triple effect: it dissolves existing dental plaque (a complex of natural enzymes), inhibits the growth of new plaque (beta-caryophyllene), maintains the balance of the oral microbiome (prebiotics, beta-caryophyllene), and freshens breath (sage extract).

CARYODENT® FINGER WIPES:



50 pcs.



CARYODENT® PROLIQUA:



vol. 250 ml



Comfortable finger pads with protrusions soaked in cetylpyridinium chloride solution and oregano oil (source of β-caryophyllene) allow for gentle teeth cleaning (removal of dental plaque, balancing of the oral microbiome)

Drinking water additive based on β-caryophyllene, brown algae and pomegranate extract, reduces the formation of dental plaque, regulates the oral microbiome and freshens breath

STEP INTO THE FUTURE OF CANCER DIAGNOSTICS!



VET EXPERT K9-LIQUIDX CANINE CANCER CHECK

Join the revolution in veterinary
diagnostics and discover our
cutting-edge solution!

An innovative, precise test utilizing liquid biopsy and next-generation sequencing (NGS) to support early detection and continuous monitoring of canine cancer.

Have questions or want to integrate this test into your clinic?
Contact your local distributor or reach us directly at: cc@vetexpert.pl