Update on Cancer Treatment in Exotics

Ashley Zehnder, DVM, PhD, DABVP(avian)[a,*],
Jennifer Graham, DVM, DABVP(avian/exotic companion mammal), DACZM[b],
Gunther Antonissen, DVM, MSc, PhD[c,d]

KEYWORDS

• Exotics • Cancer • Therapeutics • Monitoring

KEY POINTS

- Cancer therapy in exotic species is heavily reliant on extrapolation from treatment recommendations for humans, dogs, and cats.
- The primary literature available for cancer in exotics is minimal and primarily comprises single case reports or small case series.
- The basic principles of cancer treatment do not vary across species and should be adhered to with modifications made for specific species requirements.
- Exotic clinicians should work closely with medical, surgical, and radiation oncologists to ensure the best care for their patients.
- There is an urgent need for exotic clinicians to be more collaborative and share their cancer cases to improve care for patients.

INTRODUCTION

Treatment options for animals with cancer are rapidly expanding, including in exotic animal medicine. Only limited information is available, however, about treatment effects in exotic pet species beyond individual case reports. Consequently, most cancer treatment protocols in exotic animals are extrapolated from those described in humans, dogs, and cats. Practical limitations, however, as well as anatomic or physiologic differences can complicate the application of certain cancer treatment modalities in exotic species. This review provides an overview and update on cancer treatment in exotic animal species, including the various considerations that are

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[a] Department of Biomedical Data Science, 1265 Welch Road, Stanford, CA 94305-5464, USA; [b] Department of Clinical Sciences, Cummings School of Veterinary Medicine, Tufts University, 200 Westboro Road, North Grafton, MA 01536, USA; [c] Department of Pharmacology, Toxicology and Biochemistry, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium; [d] Department of Pathology, Bacteriology and Avian Diseases, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium
* Corresponding author.
E-mail address: azehnder.dvm@gmail.com

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important during the initial diagnosis, therapeutic planning, and monitoring of the exotic cancer patient.

TUMOR STAGING

Signalment, history, and thorough physical examination are important parts of the initial clinical evaluation of exotic patients with tumors. Because many tumors tend to affect animals of a particular age, gender, or species, collection of this information is vital. Diet history can help identify potential risk factors for neoplasia related to malnutrition; for example, in epidemiologic studies, the intake of carotenoid-rich fruits and vegetables has been correlated with protection from some forms of cancer[1] and it is suspected that chronic hypovitaminosis A may be a risk factor for development of squamous cell carcinoma (SCC) in pet birds.[2] Underlying viral disease is linked to cancers in a variety of species, for example, cholangiocarcinoma in Amazon parrot species with psittacid herpesvirus, lymphoproliferative disease in mice with murine leukemia virus, fibropapillomas in sea turtles with herpesvirus, and walleye dermal sarcoma retrovirus in fish, among others.[3–6] Ultraviolet light radiation has been linked to neoplastic disease in many species.[7–9] Reproductive history is important because chronic egg laying is a risk factor for development of ovarian/reproductive cancers.[10] Previous infection with *Macrorhabdus ornithogaster* may increase the risk of proventricular adenocarcinoma in budgerigars; therefore, a history of chronic macro rhabdiosis infection should not be overlooked.[11] Additionally, any chronic nonhealing wound or areas subject to repeated trauma or chronic inflammatory conditions may be at risk for development of neoplasia. In addition to revealing risk factors for neoplastic disease, patient evaluation is essential to determine the course of action. For example, it is important to rule out underlying (and potentially zoonotic) disease, such as chlamydiosis, salmonellosis, or mycobacteriosis, prior to the use of immunosuppressive agents. Similarly, underlying metabolic disease, including renal or hepatic disease; heart disease, including atherosclerosis; and other organ dysfunction may alter prognosis and a patient's ability to tolerate treatment.

For any exotic species with a suspected tumor, histologic or cytologic diagnosis of the tumor is recommended to determine (if possible) the tissue of origin and grade of tumor. Cytology can help differentiate neoplastic from non-neoplastic lesions and may broadly indicate tumor type, but accurate histogenesis and tumor grading require histology, with an exception of purely hematopoietic tumors, such as leukemias.[12] Special stains, including immunohistochemistry, may be needed to further determine various cellular antigens and cell of origin (discussed later). Mitotic index may can help determine tumor grade, but there is no clear evidence from the exotic species literature that mitotic index is prognostic.

The TNM approach, developed by the World Health Organization, is used in mammalian species to stage solid tumors and has been adapted for evaluation of disseminated tumors, such as lymphoma.[12] The TNM approach evaluates the primary tumor (T), presence or absence of metastatic disease in local and regional lymph nodes (N), and presence or absence of metastatic disease within the rest of the body (M). For exotic species that lack lymph nodes (birds, reptiles, and fish), this general concept can be adapted using a TM approach to evaluate tumors to best determine extent of disease and determine treatment options (**Fig. 1**). Because there is no clinical evidence to support the use of more precise tumor scales like those developed for specific tumors in human and companion animals, the authors recommend a more general staging technique that considers the overall health of the animal, in addition to details about the primary tumor and metastatic lesions. Once additional

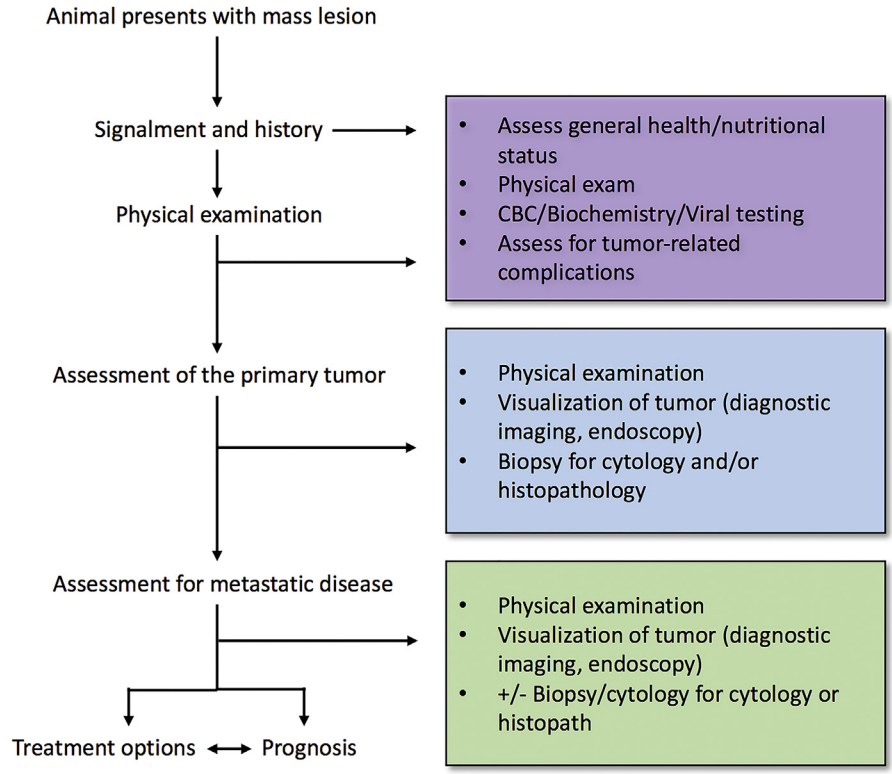

Fig. 1. Algorithm for TM tumor staging in exotic animal patients without lymph nodes. (*Adapted from* Zehnder A, Graham J, Reavill DR, et al. Neoplastic diseases in avian species. In: Speer B, editor. Current therapy in avian medicine and surgery. 1st edition. St Louis [MO]: Elsevier; 2016. p. 114; with permission.)

evidence on tumor types and outcome data are gathered, better predictions on prognosis based on tumors at their initial presentation can be made.

TM Approach

In evaluation of the primary tumor (T), the tumor is sampled by way of aspirates for cytologic diagnosis or biopsy for histologic diagnosis. In some situations, complete surgical excision of the mass may be the best option for diagnosis and treatment if disease is localized. The extent of the tumor can be evaluated by clinical examination of the patient but disease may extend beyond visible margins. Diagnostic imaging techniques, such as plain and contrast radiography, ultrasonography, CT, MRI, and endoscopy, can help assess extent of the tumor, depending on the tumor site. Objective tumor description, including specific location and measurement, in 3 planes whenever possible, should be recorded to monitor patient response. Two recent publications have provided avian body maps for use to describe more completely the location of tumors,[13,14] and maps for dogs and cats can often be adapted for many small mammal species.

In evaluation for metastatic disease (M), although the lung can be a common site for distant metastatic disease, other sites include the skin, liver, kidneys, bone, brain/nervous tissue, and spleen.[13] Physical examination may suggest metastases

(for example, cutaneous masses), but diagnostic imaging techniques, as described previously, are generally required to evaluate for metastases. Multiple radiographic views can help evaluate for metastatic disease but CT scan is generally more sensitive for evaluation of metastatic disease compared with radiographs in many species. Radiographs may show changes in the size of shape of the liver, spleen, lymph nodes, and kidneys, but ultrasound-guided aspirates or endoscopic biopsies may be required to determine extent of disease into these organs. Bone marrow aspiration is recommended for staging and diagnosing disseminated diseases like lymphoma or leukemia. More advanced imaging modalities, including MRI, PET scan, and technetium (^{99m}Tc) bone scan, have been used to evaluate for metastatic disease in a variety of species.[13,15]

CLINICAL PATHOLOGY

Complete Blood Cell Count

A complete blood cell count (CBC) should be performed as part of a minimum database collection on any patient evaluated for cancer diagnosis or treatment. Anemia or leukopenia could indicate bone marrow or splenic disease. Leukocytosis with a neutrophilia or heterophilia with or without evidence of toxicity or a left shift may indicate a concurrent infection or infection related to the tumor itself, and appropriate antibiotic therapy should be instituted based on the site of the infection (if known) and, ideally, culture and sensitivity. Chemotherapy agents are generally most toxic to rapidly dividing cells so toxicity to the bone marrow and gastrointestinal (GI) tract is a concern. CBCs should be monitored and treatment should be delayed if the heterophil or neutrophil count is too low, that is, less than 2000 cells/μL, as recommended in dogs and cats.[15,16]

Biochemistry

Similar to CBC, biochemistry profile is recommended as part a minimum database collection. Renal or hepatic enzyme elevation may indicate organ involvement or dysfunction and may preclude use of certain chemotherapeutic drugs. Nevertheless, these tests rarely provide definitive information as to the type of cancer or whether metastasis is present.

IMAGING MODALITIES

Imaging often is essential in determining both the resectability of a primary tumor as well as identification of suspected metastatic lesions. This information is crucial for devising a rational treatment plan for a veterinary cancer patient. Radiographs of the thorax are valuable in determining the clinical stage of disease in mammals. To assess the lungs properly in mammals, 3 views should be obtained—both left and right lateral views as well as a ventrodorsal view, and these recommendations can be helpful for nonmammalian exotic patients as well. Conventional radiography, preferably with high-detail film, may provide adequate diagnostic imaging for nasal and oral tumors, although the extent of disease may not be fully elucidated. Ultrasonography allows evaluation of the architecture of abdominal viscera and has largely replaced radiographs in staging of mammalian cancer patients with abdominal neoplasia. CT has become more widely available for veterinary use, particularly at teaching institutions and large specialty practices. CT can be helpful to evaluate tumors within the nasal and oral cavities. CT is particularly useful when a veterinarian is trying to determine tumor margins prior to surgery or radiation therapy. CT imaging of the lungs, often accomplished with controlled ventilation, provides increased

sensitivity in detecting small pulmonary nodules as well as enhanced discrimination of lesion location[17,18] compared with traditional radiography.

MRI is often the modality of choice for imaging tumors of the brain and spine. Lesions of the brainstem may require MRI for diagnostic quality. In addition to CT, MRI is useful when a veterinarian is trying to determine tumor margins prior to surgery or radiation therapy. MRI is often considered more sensitive in detecting tumor margins in soft tissues. Due to the slow speed of image acquisition, MRI has limited utility in imaging of the thorax in mammals and birds due to movement of the heart and lungs. PET is used to stage, plan surgery, evaluate response to therapy, and detect relapse of various neoplastic conditions. PET has been used to evaluate 2 cases of avian neoplasia, and normal PET image acquisition in Hispaniolan Amazon parrots has been described.[19]

TREATMENT MODALITIES

Although there are abundant articles on toxicity of chemotherapeutic agents in laboratory animals, these studies are generally performed in healthy animals at nontherapeutic doses in a laboratory setting and can be hard to extrapolate to pet species. Because information regarding the treatment effects in exotic pet species is scarce and generally limited to individual case reports, cancer treatment protocols in exotic animals are generally extrapolated from those described in humans, dogs, and cats.

There are some important differences, however, between exotic species versus dog and cat patients. Notably, many exotic patients presenting with tumors are small and vascular access is challenging for intravenous administration of chemotherapeutics. Nevertheless, the use of vascular access ports has been reported in exotic species, including ferrets, birds, rabbits, rodents, and reptiles, and can be considered in situations where repeated vascular access is necessary (eg, to administer medication or sample blood to monitor systemic response to therapy [**Fig. 2**]).[15,20] Due to their small size, vascular access ports in exotic patients are prone to clotting, and appropriate heparin locking is required to maintain function.

Depending on the type of neoplasia, a variety of treatment modalities can be considered for exotic species. Oral chemotherapeutics used in humans, dogs, and cats can be used in exotic animals, but compounding into appropriate doses may be necessary. If a medication needs to be swallowed whole versus crushed, use in exotic

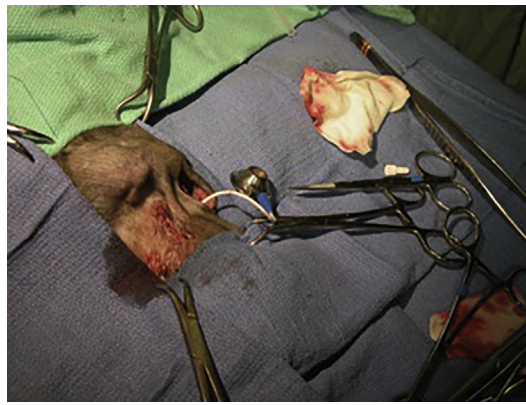

Fig. 2. Vascular access port placement in a wolf with a myxosarcoma. (Courtesy of Tara Harrison, DVM, MPVM, DACZM, DACVPM, North Carolina State University).

species may not be possible. Intratumoral chemotherapy consists of injecting antineoplastic drugs into the tumor and nearby tissue and can be used in combination with surgery or radiation therapy. Slow-release formulations, such as sesame oil emulsions or collagen matrix, can optimize pharmacokinetics to allow for more prolonged exposure of the drug to tissue.

Radiation therapy is a common treatment modality in some exotic animal tumors, including thymoma in rabbits. Radiation therapies available for use in veterinary patients include teletherapy, plesiotherapy, brachytherapy, and systemic radiation therapy with radionucleotides.[21] In some situations, radiation therapy is combined with surgery or chemotherapy to maximize the chance for tumor response to therapy. Hormonal therapy, phototherapy, hyperthermia, immunotherapy, nonsteroidal therapy, antiangiogenic antibiotics, metronomic chemotherapy, and complementary and alternative therapy are other considerations for treatment of exotic neoplasia.

TRANSLATING CANCER THERAPIES TO EXOTICS

Metabolism

Birds have a high metabolic rate compared with most mammals but pharmacokinetic data has been obtained with some chemotherapeutics in a limited number of avian species. Results of these studies show that extrapolation of dosing regimens from mammals to avian species is at least a good starting point.[22] The opposite may be true for reptiles, and doses may need to be reduced or dosing intervals made less frequent as for other types of medications, such as antibiotics. Studies to determine appropriate metabolic scaling of chemotherapeutics for reptiles are, however, lacking. For poikilotherms, the ambient temperature and availability of appropriate temperature gradients within the enclosure are important for adequate drug metabolism. Better information is available in the laboratory animal literature for small mammals, but doses and dose intervals often still need to be adjusted from dog and cat doses.

Vascular Support, Renal/Hepatic Excretion

Birds and reptiles have a renal portal system and, in general, injection of chemotherapeutic drugs into leg vasculature should be avoided to prevent excretion of these agents before they enter the full circulatory system. Additionally, caution should be taken with the injection of any nephrotoxic agents into the leg vasculature for the same reason.

Risks of Corticosteroids and Immunosuppressive Agents

Any immunosuppressive therapy should be used with caution in most exotic species. Because of the high number of zoonotic diseases reported in exotic species, this issue must be taken into consideration when using immunosuppressive therapy in these patients or if owners are immunocompromised. Steroid therapy is not without risk of immunosuppression and secondary infection in exotic patients. Prophylactic antibiotic and antifungal therapy may be prudent whenever immunosuppressive drugs are used in these species. Certain species are known to harbor chronic infections that can exacerbate, flare up, or manifest clinically after use of steroids (eg, *Escherichia cuniculi* infections in rabbits). Thus, care should be taken before starting steroids in any exotic species. The exception to this is ferrets, which seem to tolerate steroid therapy well, and steroids can be used to help manage common diseases, like GI lymphoma.[23,24]

CHEMOTHERAPY

Although the use of chemotherapy in exotic animal oncology is increasing, the information in literature is limited and mainly based on case study findings and extrapolation from the human literature and the treatment of dogs and cats. Dosing of antineoplastic drugs should be done carefully because of their narrow therapeutic-toxic range. Therefore, it is of great importance to understand the basic mechanisms of action and potential toxicities before attempting to treat any animal species with chemotherapy (**Table 1**). Because recent reviews have discussed the basic pharmacology of common chemotherapeutics, this point is not be belabored in this article.[20] Currently, there is a growing interest in combining anticancer drugs aiming at maximizing efficacy while minimizing systemic toxicity through the delivery of lower drug doses. Combining 2 or more agents has a greater response than when used alone. The development of a multiagent chemotherapy protocol is based on selecting agents that act at different phases of the cell cycle (**Fig. 3**), have independent mode of actions, have synergistic effects to overcome drug resistance, and vary in their toxicities. Chemotherapy drugs can be administered by multiple routes, including orally, subcutaneously, intralesionally, intravenously, and intraosseously (**Fig. 4**). In particular, repeated intravenous administration might be difficult in many exotic animal species because of limited vascular access and because of the high vesicant and irritant properties of many chemotherapy drugs. In human medicine, there is a major trend in the development of oral chemotherapy, driven by pharmacoeconomic issues as well as patient convenience and quality of life. The availability of more oral chemotherapeutics will facilitate future usage of chemotherapy in exotic animals. Regardless of the route chosen, clinicians administering chemotherapy need to take appropriate precautions to protect themselves, patients, and owners from contact with potential toxic chemotherapeutics (**Fig. 5**).[20]

Chemotherapeutics are commonly dosed based on the body surface area (BSA) of a patient instead of the bodyweight (BW), because the BSA is considered a better indicator of the metabolic mass.[77] Because knowledge in exotic animal cancer treatment is limited, the use of BSA to derive interspecies equivalents for therapeutic dosages is opening treatment perspectives. Misunderstood and misinterpreted use of BSA conversions, however, may have unfavorable consequences, including underdosing, leading to treatment failure, and overdosing, inducing unexpected severe or even deadly adverse effects. Therefore, dose extrapolation between different animal species should be based on more advanced allometric and physiologically based pharmacokinetic modeling.[146] Recently, Antonissen and colleagues[22] demonstrated by allometric scaling a clear correlation (R^2>0.97) between BW and the elimination half-life ($T_{1/2el}$) of carboplatin in different avian species, expressed by the formula, $T_{1/2el\ carboplatin} = 0.1147$ (log value of BW)$^{0.3046}$. $T_{1/2el}$ could also be scaled with an acceptable correlation ($R^2 = 0.83$) in different mammalian species (rats, cats, dogs, and humans)[147–150] and different avian species (budgerigar, pigeons, ducks, cockatoos, and chickens).[22,137] Allometric scaling within 1 animal class is, however, preferred. Furthermore, carboplatin clearance is highly correlated with the animals' glomerular filtration rate. Taking into account the enormous differences in physiology between different exotic animal species, interanimal class dose extrapolation of chemotherapeutics is related to a major risk of therapy failure.

EMERGING MOLECULARLY TARGETED AGENTS

Most traditional chemotherapeutics have been drugs or other therapies that target cancer cells by killing rapidly dividing cells or killing all the cells in a particular area

Table 1
Chemotherapy agents that can be used in exotic animal medicine

Chemotherapy Agent	Mode of Action/Pharmacokinetics		Principal Indications	Toxicities/Side Effects	Administration Routes	Dosage	Case Reports
Nitrosoureas	• Highly lipophilic, which enter cells through passive diffusion • Undergo bioactivation by cytochrome P450 enzymes in the liver • These metabolites cause alkylation and cross-linking of DNA (at the O_6-position of guanine-containing bases) and RNA, thus inducing cytotoxicity. • Also inhibit several key processes, such as carbamoylation and modification of cellular proteins • Urinary excretion, with minimal biliary excretion and GI reabsorption • Cell-cycle nonspecific	Lomustine (CCNU)	• Lymphoma • Mass cell tumor • Histiocytic sarcoma • Brain tumor	• Myelosuppression • GI toxicity • Sores in oral cavity • Pulmonary toxicity • Renal toxicity • Hepatotoxicity	PO	30–90 mg/m^2 Interval 3–8 wk[30–32]	[20,25–29]
		Carmustine (BCNU)	• Lymphoma • Neurologic tumor	• Myelosuppression • Pulmonary toxicity • GI toxicity	IV, local delivery	50 mg/m^2 Interval 6 wk[33,34]	N/A
Nitrogen mustard alkylating agents	• Bifunctional alkylating agents • Mustards react with the N7 atom of purine bases, especially when they are flanked by adjacent guanines, inducing DNA strand breakage, cross-linking strands of DNA and ring cleavage. • Cell-cycle nonspecific • Well absorbed after PO administration • Excretion: small fraction a dose eliminated unchanged by urinary excretion, with minimal biliary excretion, majority eliminated by metabolic transformation[35–37] • Cyclophosphamide and ifosfamide: parent drug is relatively inactive, undergo bioactivation via hydroxylation by cytochrome P450 enzymes in the liver with formation of (iso)phosphoramide mustard • Chlorambucil and melphalan: direct alkylating ability • Sensitive to acquired tumor cell resistance by increased gluthatione conjugation[38]	Cyclophosphamide	• Lymphoma • Carcinoma • Sarcoma	• Myelosuppression[39] • GI toxicity • Renal toxicity • Urothelial toxicity (+ furosemide,[48] mesna[49]) • Feather abnormalities[51]	PO, IV, IO	10–80 mg/m^2 PO 3–4 consecutive d/wk[40,46,47] 100–200 mg/m^2 IV, IO Interval 1–3 wk 15 mg/m^2 PO daily (metronomic)[47,50]	[20,40–45]
		Ifosfamide	• Lymphoma • Sarcoma	• Myelosuppression • GI toxicity • Renal toxicity • Urothelial toxicity (+ furosemide,[54] mesna[55]) • Neurotoxicity	PO, IV	375–900 mg/m^2 IV Interval 3–4 wk[52,53]	N/A
		Chlorambucil	• Lymphocytic leukemia • Lymphoma • Mast cell tumor • Myeloma • Ovarian adenocarcinoma	• Myelosuppression • GI toxicity • Renal toxicity • Hepatotoxicity • Pulmonary toxicity • Alopecia	PO	10–20 mg/m^2 or 1–2 mg/kg Interval 0.5–2 wk[56,61] 4 mg/m^2 PO daily metronomic[62,63]	[26,40,42,56–60]
		Melphalan	• Myeloma • Lymphocytic leukemia • Lymphoma • Ovarian adenocarcinoma	• Myelosuppression[64] • GI toxicity • Pulmonary toxicity	PO	0.1 mg/kg daily for 10 d followed by 0.05 mg/kg per day or pulse dose administration of 3–7 mg/m^2 for 5 d in 3-wk cycle[65–67]	[65]

Antitumor antibiotics	Anthracyclines and anthracenediones: • Drugs first extracted from *Streptomyces* spp • Intercalation into DNA and disruption of topoisomerase-II–mediated DNA repair • Iron-mediated generation of free oxygen radicals that damage the DNA, proteins, and cell membranes • Cell-cycle nonspecific, although maximally cytotoxic during S phase • Low oral bioavailability • Doxorubicin is metabolized extensively to doxorubicinol by the ubiquitous aldo-keto reductase enzymes; by interfering with the iron and calcium regulation, this metabolite is important for doxorubicin cardiotoxicity.[68,69] • Biliary excretion, with minimal urinary excretion	Doxorubicin	• Lymphoma • Sarcoma • Carcinoma	• Cardiotoxicity[72] • Myelosuppression • GI toxicity • Renal toxicity • Hypersensitivity (mainly GI and skin related) • Alopecia • Perivascular damage with extravasation	IV, IO	20–60 mg/m^2 or 1–2 mg/kg Interval 2–3 wk[77–80]	[20,40,41,43,68,73–76]
		Epirubicin	• Lymphoma • Sarcoma • Carcinoma	• Less cardiotoxic than doxorubicin[81,82] • Similar to doxorubicin	IV	30 mg/m^2 Interval 3 wk[83]	N/A
		Mitoxantrone	• Lymphoma • Sarcoma • Carcinoma	• Less cardiotoxic than doxorubicin • More hepatotoxic than doxorubicin[87] • Myelosupression • GI toxicity	IV, local delivery[84–86]	2.5–5 mg/m^2 IV Interval 3 wk[88,89]	N/A
	Chromomycins: • Drug first extracted from *Streptomyces* spp • Inhibit RNA synthesis by binding to guanine residues and inhibiting DNA-dependent RNA polymerase • Intercalation into DNA and disruption of topoisomerase-I and topoisomerase-II–mediated DNA repair[70] • Cell-cycle nonspecific • Biliary excretion, with minimal urinary excretion	Actinomycin D or dactinomycin	• Lymphoma	• Myelosuppression • GI toxicity • Perivascular damage with extravasation	IV	0.5–0.8 mg/m^2 Interval 3 wk[90,91]	N/A
	Miscellaneous: • Drug first extracted from *Streptomyces* spp • Forming an iron-oxygen-bleomycin complex that then forms free radicals, which cause single and double-stranded DNA breaks • Cell-cycle specific (G2 and M phase)	Bleomycin	• Lymphoma • Fibropapiloma • SCC	• Pulmonary toxicity • Stomatitis • Hyperpigmentation of skin • Hypersensitivity	IV, IM, SC, local delivery	10–20 U/m^2 for 3–9 d, then weekly	[20,92,93]

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Table 1
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Chemotherapy Agent	Mode of Action/Pharmacokinetics		Principal Indications	Toxicities/Side Effects	Administration Routes	Dosage	Case Reports
	• Metabolized by a cysteine protease hydrolase enzyme in normal tissues. The enzyme replaces a terminal amine with a hydroxyl, thereby inhibiting iron binding and cytotoxic activity. The low enzyme concentration in skin and lung may explain the unique sensitivity of these tissues to bleomycin toxicity.[71] • Mainly excreted with urine						
Antitubulin agents	Vinca alkaloids • Vincristine and vinblastine first extracted from periwinkle plant (*Catharanthus rosea*); vindesine and vinorelbine are semisynthetic derivatives of vinblastine. • Bind to the free tubulin-dimers, inhibiting the formation of microtubule—more specifically, the forming of the mitotic spindles—and thereby mitosis • Cell-cycle phase specific (M phase) • Metabolized in liver by cytochrome P450, and concomitantly administered drugs may either competitively inhibit or induce cytochrome P450 clearance of vinca alkaloids. • Largely excreted in the bile and feces, with little renal excretion[94,95]	Vincristine	• Lymphoma • Mast cell tumor	• GI toxicity • Myelosuppression • Neurotoxicity • Perivascular vesicant • Alopecia	IV, IO, local delivery	0.1–0.75 mg/m^2 Interval 1–2 wk	[20,40,41,43,44,57,101,102]
		Vinblastine	• Mast cell tumor[103] • TCC[104]	• GI toxicity • Myelosuppression • Perivascular vesicant	IV	2.0–3.5 mg/m^2 Interval 1–2 wk[103,147]	
		Vinorelbine	• Lymphoma • Mast cell tumor • TCC • Histiocytic sarcoma • Pulmonary carcinoma	• Myelosuppression • Perivascular vesicant[105] • Less neurotoxic than vincristine	IV	15 mg/m^2 Interval 1–2 wk[105,107,108]	[105,106]
	Taxanes • Complex diterpenes (hydrocarbons) originally identified from plants of the genus *Taxus* (yews) • As opposed to vinca alkaloids, taxanes increase microtubule stability and prevent dipolymerization, which causes tubulin bundling. • Cell-cycle phase specific, cells are arrested in G2/M phase, which is known to be the most radiosensitive phase of the cell cycle.	Paclitaxel	• Carcinoma • Sarcoma	• Myelosuppression • Hypersensitivity • Neurotoxicity • Alopecia • GI toxicity	IV, PO	130–150 mg/m^2 IV Interval 3 wk[96,109]	N/A
		Docetaxel	• Carcinoma • Sarcoma	• Myelosuppression • Hypersensitivity • GI toxicity	IV, PO	20–30 mg/m^2 or 1–2.5 mg/kg IV Interval 3 wk[111,112]	[110]

• Widely distribute into most tissues, except central nervous system • Substrates for the P-glycoprotein transporters, which interfere with their GI absorption—novel taxane analogs have been developed in human medicine that are poor substrates for P-glycoprotein and have higher oral bioavailability,[96] or taxane oral bioavailability increases by coadministration of competitive substrates for example, cyclosporine A.[97] • Largely excreted in the bile and feces, with little renal excretion						
Topoisomerase interactive agents • Semisynthetic derivatives of podophyllotoxin • Inhibit DNA synthesis by forming a complex with topoisomerase-II and DNA. This complex induces break in double-stranded DNA and prevents repair by topoisomerase-II binding. • Cell-cycle phase specific (late G2 and early S phases) • Oral bioavailability is highly variable. Substrates for the P-glycoprotein transporters, which interfere with their GI absorption—oral bioavailability increases by coadministration of competitive substrates, for example, cyclosporine A.[98,99] • Converted to an O-demethylated metabolite by hepatic microsomal cytochrome P450, which has a similar potency at inhibiting topoisomerase-II and is more oxidatively reactive than the parent drug.[100] • Mainly excreted with urine	Etoposide	• Hemangiosarcoma[113] • Osteosarcoma[115] • Lymphoma[114] • Lung carcinoma	• Myelosuppression • Hypersensitivity • GI toxicity • Cardiotoxicity	IV, PO	50 mg/m^2 PO daily for 3 wk, 25 mg/m^2 for 4 consecutive days IV[113,114]	N/A
	Teniposide	• Leukemia • Lymphoma • Lung carcinoma	• Myelosuppression • Hypersensitivity • GI toxicity • Cardiotoxicity	IV, PO	20 mg/kg IV or PO single administration 6.5 mg/kg IV Interval 3 d[116,117]	N/A

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Table 1
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Chemotherapy Agent	Mode of Action/Pharmacokinetics		Principal Indications	Toxicities/Side Effects	Administration Routes	Dosage	Case Reports
Antimetabolites	General • Similar to endogenous metabolites, which are needed for normal biochemical activities involved in normal cell function and replication • Interfere directly with normal cell metabolism, interacting directly with specific enzymes by either inhibiting enzyme production or by producing a nonfunctional end product blocking cell processes dependent on that enzyme or end product, inhibiting protein, RNA or DNA synthesis • Cell-cycle phase specific (S phases)						
	Pyrimidine antagonists • Analogs of uracil or cytosine • 5-Fluoropyrimidines are structural pyrimidine base analog of uracil, inhibiting the enzymatic conversion of uracil to thymidine, inducing failure of normal DNA synthesis, faulty translation of RNA, and finally cytotoxicity of the rapidly dividing cancer cells. • Clearance of 5-fluoropyrimidines mediated by cytosolic enzyme dehydropyrimidine dehydrogenase–saturable process: impact on efficacy and safety bolus vs infusion administration • Gemcitabine is activated by being triphosphorylated on transport into the cell, which is catalyzed by the enzyme deoxycytidine kinase. Triphosporylated gemcitabine can masquerade as cytidine and is incorporated into new DNA strands. By masked chain termination	5-Flurouracil	• Carcinoma	• Myelosuppression • GI toxicity • Cardiotoxicity[124,125] • Neurotoxicity	IV, local delivery	150–200 mg/m^2 IV Interval 1 wk[123] 1.47 mg/kg intralesionally Interval 3 wk[121,122]	[121,122]
		Gemcitabine	• Lymphoma • Carincoma	• Myelosuppression • GI toxicity	IV	275–400 mg/m^2 Interval 2–3 wk Low dosage of 40 mg/m^2 as radiosensitizer[118,126]	[20]
		Cytarabine	• Lymphoma • Leukemia	• Myelosuppression • GI toxicity	IV, SC	100–150 mg/m^2 IV or SQ for 4–5 consequent days repeat interval 3–4 wk[127,128]	[44,127]

	by a normal nucleoside base aside gemcitabine, normal cell repair system not activated. Consequently, due to this irreparable DNA error, further DNA synthesis is inhibited and leads to cell death.[118] • Cytosine arabinoside or cytarabine is a deoxycytidine base compound, which is phosphorylated in cells to the active metabolite arabinosylcytosine triphosphate, which is a competitive inhibitor of DNA polymerase α, and is incorporated into DNA and causes strand termination. Consequently, the cancer cell is unable to divide.[119] • Low oral bioavailability • Mainly excreted with urine[120]						
	Folate antagonist • Methotrexate is a competitive inhibitor of the enzyme folic acid reductase, preventing reduction of dihydrofolate to tetrahydrofolate, which is necessary for the synthesis of thymidylate, an essential component of DNA.[119] • High oral bioavailability • Largely excreted by urine but also substantial biliary excretion	Methotrexate	• Lymphoma	• Myelosuppression • GI toxicity	PO, IV	2,5–5,0 mg/m^2 PO Interval 1–2 d[123] 0.3–0.8 mg/m^2 IV Interval 1–3 wk	[40]
Corticosteroids	• Induce apoptosis of hematopoietic cancer cell by interaction with glucocorticoid receptor • Inhibit inflammatory and immune responses, most likely through alteration of cellular transcription and protein synthesis as well as through effects on lipocortins, which inhibit the release of arachidonic acid • Provide palliative appetite and anti-inflammatory support • Very high oral bioavailability	Prednisolone/ prednisone	• Lymphoma • Mast cell tumor • Leukemia • Brain tumor • Insulinoma	• Polyuria/polydipsia • Polyphagia • GI toxicity • Hepatotoxicity • Hyperadrenocorticism • Dull hair coat • Pancreatitis	PO	0.5–2 mg/kg BW PO daily	[20,26,41–44,58,76]

(*continued on next page*)

Table 1
(continued)

Chemotherapy Agent	Mode of Action/Pharmacokinetics		Principal Indications	Toxicities/Side Effects	Administration Routes	Dosage	Case Reports
	• Avian patients: long-term usage predisposing for aspergillus infection or severe immune suppression • Do no use in combination with NSAIDs: increased toxicity • Cell-cycle nonspecific						
Platinum	• Binding covalently to the N7 position of the imidazole ring of the purine bases of DNA, primarily guanine, and to a lesser extent adenine, forming monofunctional or bifunctional DNA intrastrand and interstrand adducts. This activates various signal-transduction pathways, such as those involved in DNA damage recognition and repair, cell-cycle arrest, and programmed cell death/apoptosis.[129] • Platinum drugs (II), such as cisplatin, carboplatin, and oxaliplatin, are not orally bioavailable due to their chemical reactivity, poor absorption, and severe GI side effects. • Platinum (IV) compounds, such as satraplatin and tetraplatin, can be administered orally. These platinum compounds are prodrugs; once they enter cancer cells, they are reduced and activated by cellular reductants and form active complexes. These compounds are still under investigation.[130] • Mainly excreted with urine—platinum drug clearance is strongly associated with glomerular filtration rate. Carboplatin dosing using a pharmacologic formula is based on glomerular filtration rate and produces accurate targeting of the carboplatin AUC.[131] • Cell-cycle nonspecific	Cisplatin	• Carcinoma • Sarcoma	• Myelosuppression • GI toxicity • Nephrotoxicity • Ototoxicity • Pulmonary edema (species-specific, demonstrated in cats)[136]	IV, IO, local delivery	70 mg/m^2 IV Or 1 mg/kg BW IV Interval 3 wk[134] 1 mg/cm^3 intratumoral[135]	[20,132,133]
		Carboplatin	• Carcinoma • Sarcoma	• Myelosuppression • GI toxicity • Less neurotoxic/ototoxic than cisplatin[142]	IV, IO, local delivery	125–300 mg/m^2 IV Or 5–10 mg/kg BW IV[22,137] Interval 3 wk 1.5 mg/cm^3 intratumoral[143]	[20,22,74,137–141]

L-Asparginase	• Enzyme purified from the bacterium *E coli* or *Erwinia carotovora* • Asparaginase hydrolyzes L-asparagine to L-aspartic acid and ammonia in leukemic cells, resulting in depletion of asparagine, inhibition of protein synthesis. Asparagine is critical to protein synthesis in leukemic cells, because these cells lack the enzyme asparagine synthase. • Pegaspargase: polyethylene glycol-conjugated asparaginase is slow-release form of *E coli* asparaginase • L-Asparaginase resistance in tumor cells, for example, by development of antiasparginase antibodies, or de novo biosynthesis of aspargine • No antigenic cross-reactivity between *E coli* and *E carotovora* asparaginase • No oral administration: denaturation and peptidase digestion within GI tract • Cell-cycle specific (G1 phase)[119]	L-Asparginase	• Lymphoma • Leukemia	• Hypersensitivity[144] • GI toxicity • Coagulopathies • Pancreatitis • Hepatotoxicity • Hyperglycemia	IM, SC	400 IU/kg BW IM/SQ Or 10,000–12,000 IU/m^2 Weekly interval	[20,26,58]
Hydroxyurea	• Inhibits DNA synthesis by inhibition of ribonucleotide diphosphate reductase. Hydroxyurea inhibits the conversion of DNA bases by blocking ribonucleotide reductase, thereby preventing conversion of ribonucleotides to deoxyribonucleotides. • Hydroxyurea also inhibits the incorporation of thymidine into DNA and may directly damage DNA. • Well absorbed after oral administration • Largely excreted by urine • Cell-cycle specific (S phase)	Hydroxyurea	• Leukemia • Mast cell tumor • Meningioma	• Myelosuppression • GI toxicity	PO	30–60 mg/kg daily[145]	N/A

Abbreviations: IO, intraosseous; IV, intravenous; PO, oral; SC subcutaneous; N/A, Not Reported.

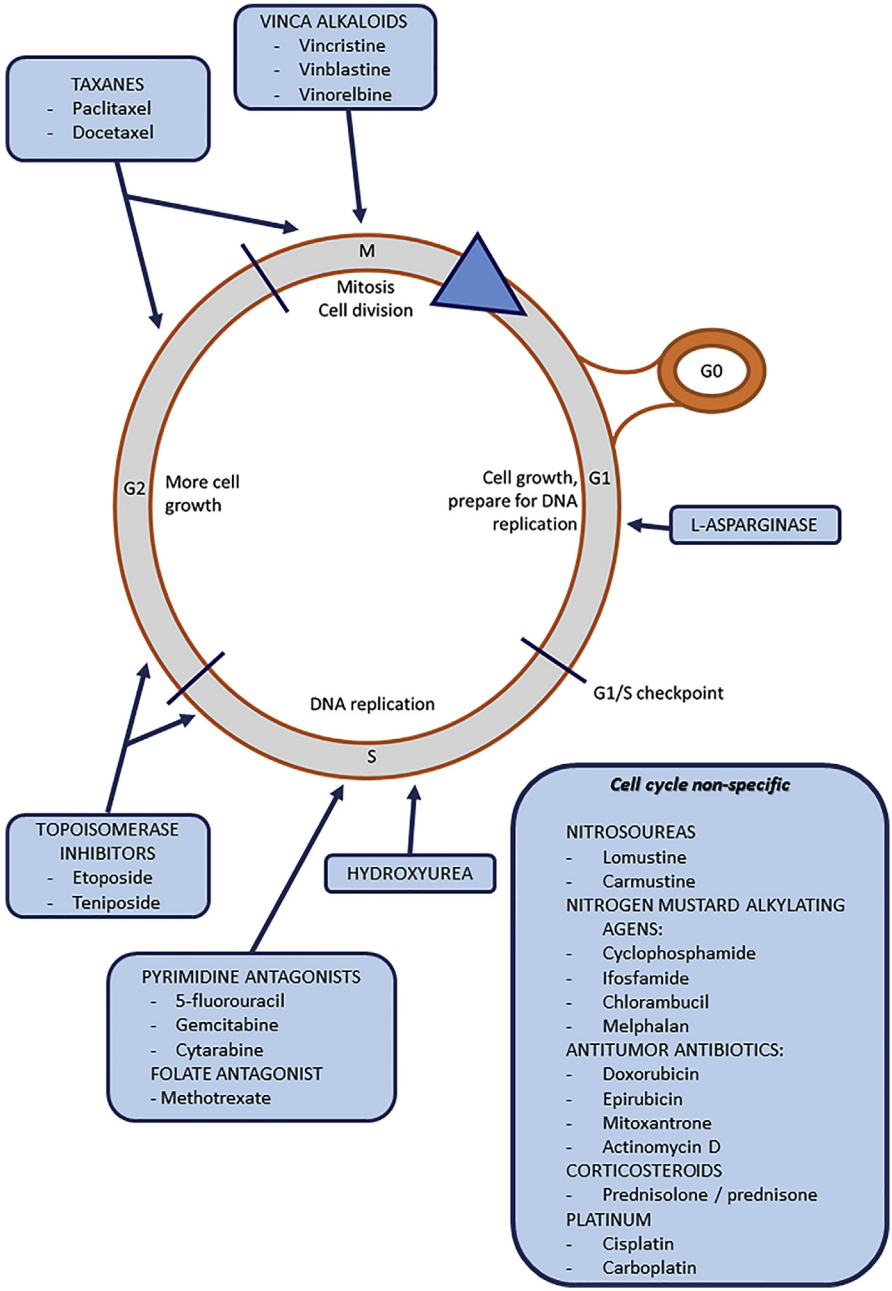

Fig. 3. Cell-cycle specific and cell-cycle nonspecific chemotherapeutic agents. Multiagent chemotherapy protocols should be based on selecting agents that act in at different phases of the cell cycle.

of the body affected by cancer. Although these treatments have certainly helped cure many patients, they also frequently have treatment-limiting side effects due to effects on normal cells. The holy grail of cancer therapy is to kill a cancerous cell while leaving

Fig. 4. Intralesional carboplatin administration to SCC in a cockatiel.

normal, healthy cells intact. New generations of targeted therapies attempt to achieve this goal through logically designed therapies targeting cancer specific mutations or cancer-specific pathways (**Fig. 6** and **Table 2**). Although many targeted agents actually affect many different receptors, with targeted therapies it becomes more important to know which particular mutations are present in a cancer cell or which cellular pathways it depends on for survival to rationally guide treatment. Although these therapies hold a great deal of promise for offering new, potentially less toxic treatments for exotic patients, it is unclear to what extent tumors in exotic species express the cellular receptors targeted by these agents. This may make it more difficult to translate new therapies emerging in human medicine (and for dogs and cats) without knowing how cancers in exotic species are alike and different. Some clinicians have begun to provide these therapies to patients when there are no other acceptable treatment options, but results from these cases are not yet available. These drugs also can have significant toxicities (see **Table 2**). Also, information on appropriate dosing for therapeutic efficacy is not at all known, and owners should always be made aware that use of these therapies in exotic species is experimental. Recording standardized

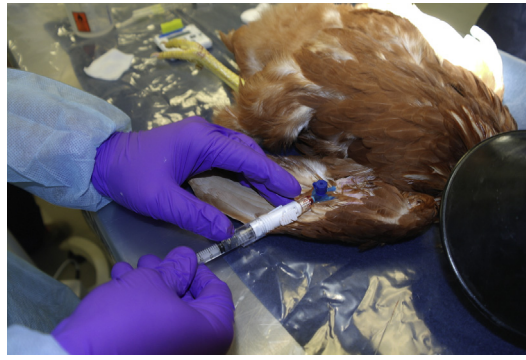

Fig. 5. Safety measures in handling chemotherapy: intravenous administration of carboplatin in a chicken. Veterinarians administering chemotherapy need to be familiar with the chemotherapeutic agents used and of safety issues for themselves, owners, and staff. Luer-Lok syringes should be used to avoid drug leakage, and all personnel handling drugs or patients receiving chemotherapeutic drugs should wear protective clothing, including gloves, eye protection, closed-toe shoes, and long sleeves.

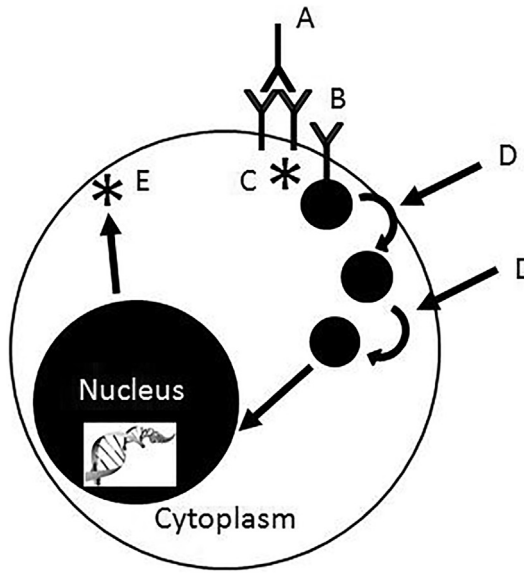

Fig. 6. Schematic of molecular targets for cancer therapy. A, antibody against cell surface receptor. B, cell surface receptor. C, small molecular inhibitor of cell surface receptor. D inhibitor of downstream pathway components. E, inhibitor of gene fusion product. (*Adapted from* Zehnder A, Graham J, Reavill DR, et al. Neoplastic diseases in avian species. In: Speer B, editor. Current therapy in avian medicine and surgery. 1st edition. St Louis [MO]: Elsevier; 2016. p. 132; with permission.)

case parameters (adverse effects and outcome information) for cases in which these agents are used is critical to evaluate their potential use in exotics species.

The types of therapies being developed for use in human and companion animals are summarized later and in **Table 2**, so that clinicians are aware of the types of therapies that may be available for treating exotic patients, with the caveat that little is known about the underlying cancer biology or the expression of certain cellular receptors in exotic species.

Tyrosine Kinase Inhibitors

There are 2 tyrosine kinase inhibitors that have been used in veterinary patients. Tyrosine kinases are cellular receptors that help normal cells and cancer cells interact with extracellular signals and are often mutated or overexpressed in multiple cancer types. The first is toceranib phosphate (Palladia), an inhibitor of the split-kinase family, which includes several growth factors implicated in cancer development: vascular endothelial growth factor receptor, platelet-derived growth factor receptor, c-kit, Flt-3, and others.[183] It was originally developed for use in mast cell tumors with an activating c-kit mutation but its role as an antiangiogenic therapy is also being studied, due to its inhibition of additional kinase family members. Toceranib has been used in a binturong (*Actictis binturong*) with renal carcinoma after nephrectomy with no discernible clinical effect but minimal adverse effects (mild inappetence).[184] In dogs, toceranib has been evaluated for safety in patients with a variety of solid tumor types[185] and found generally safe, with some mild GI effects requiring a treatment holiday. Reported side effects, however, can be as severe as GI perforation and can include other manifestations, such as lameness, hematochezia, pruritus, and localized edema (in a radiation patient).

Table 2
Summary of molecularly targeted agents

Toceranib

Combined with	Species	N	Tumor Type(s)	Clinical Effects	Adverse Events	Study Type	Citation
	Dogs	57	Various (MCT, lymphoma, STS, MMC, TCC, melanoma, OSCC, others)	ORR: 28% (highest in—55%)	Appetite loss, diarrhea, vomiting, neutropenia, grades 1 and 2, seen with daily dosing	Experimental, prospective, phase I	151
Single agent	Dogs	40	STS, TC, ASAGACA, NCA, SCC, OSA, carcinoma (various)	Clinical benefit: 90%	Majority grades 1 and 2, majority GI (52.5%), hematologic (42.5%), other effects: hypertension, PLN, lameness,	Experimental, prospective (phase I—evaluating effect of lower dose)	152
Prednisone/ hypofractionated radiation	Dogs	17	MCT	ORR: 86.7%, CR: 66.7%	GI and hepatic most common, mostly grades 1 and 2	Experimental, prospective clinical trial	153
Vinblastine	Dogs	14	MCT	ORR: 71%	Higher-grade neutropenia with combination than expected with single agent, improved with lower vinblastine doses	Experimental, prospective phase I clinical trial	154
Carboplatin/ cyclophosphamide	Dogs	126	OSA	No significant survival benefit	Grades 1 and 2 neutropenia and thrombocytopenia, trade 1 diarrhea, lethargy, vomiting most common	Experimental, prospective (randomized clinical trial)	155
Doxorubicin	Dogs	43	HSA	No significant survival benefit (compared with historical controls)	Grades 1 and 2 GI and grade 1 anemia most common	Experimental, prospective	156
Cyclophosphamide	Dogs	15	OSA, STS, HSA, LSA, MH, TCC, TC, ASAGACA, maxillary and perineum carcinoma	Decreased circulating Treg cells, increased serum concentration of IFN-γ	Grades 1 and 2, GI most common	Experimental, prospective	47

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Table 2
(*continued*)

Toceranib

Combined with	Species	N	Tumor Type(s)	Clinical Effects	Adverse Events	Study Type	Citation
CCNU	Dogs	13	Multicentric LSA, OSA, PCA, STS, MLO, carcinoma/adenocarcinoma (various)	Clinical benefit: 53.8%	Grades 3 or 4 effects: neutropenia, elevated ALT. AE more common in higher CCNU dose cohorts	Experimental, prospective (phase I—CCNU dose escalation)	[157]
Lomustine	Dogs	47	MCT	ORR: 46% (not increased over single agent studies)	Grades 1 and 2 GI, anemia, neutropenia most common, grade 4 neutropenia (n = 9)	Experimental, prospective (phase I—lomustine dose escalation)	[158]
Vinblastine	Dogs	10	TCC	No significant response (compared with historical single agent studies)		Experimental, prospective (pilot study, no internal control group)	[159]
Various	Dogs	85	ASAGACA, OSA, TC, HNCA, NCA	Clinical benefit: ASAGACA (87.5%), OSA (47.8%), TC (80%), HNCA (75%), NCA (71.4%)	AE in 77.6%, majority GI (AE not graded)	Observational, retrospective	[160]
Prednisone	Dogs	1	Chronic monocytic leukemia	Clinical remission	Not reported	Case report	[161]
Piroxicam or meloxicam	Cats	46	FOSCC	Significant increased survival rate compared with NSAID only controls	Grades 1 and 2 lethargy, anorexia, vomiting most common	Cohort, retrospective	[162]
Prednisolone or meloxicam	Cats	14	MCT, FOSCC, lymphoma, various carcinomas	Clinical benefit: 57.1%	Grade 1 neutropenia and GI AE most common, potential hepatotoxicity reported	Cohort, retrospective	[163]
Single agent	Cats	18	FISS	No measurable clinical response	Generally mild, grade 3 lymphopena and 4 ALT elevation managed with drug holidays	Experimental, prospective	[164]

Carboplatin, piroxicam	Cat	1	Tracheal adenocarcinoma	Survival: 755 d	None reported	Case report [165]
Octreotide	Cat	1	Gastrinoma	Survival: 5 mo (euthanized)	Anorexia, treatment limiting	Case report [166]
Single agent	Binturong	1	Renal carcinoma	Survival: 4 mo (euthanized)	Mild inappetence	Case report [184]

Masatinib

Combination	Species	N	Tumor Type(s)	Clinical Effects	Adverse Events	Study Type	Citation
	Dogs	202	MCT	Increased time to progression 75–118 d, more significant in naive patients	Diarrhea, vomiting most common, generally grades 1 and 2	Experimental, Double-blind, randomized, placebo-controlled phase III clinical trial	[167]
	Dogs	132	MCT	Increased survival compared with placebo (617 vs 322d)	Not discussed	Experimental, placebo-controlled trial	[168]
	Dogs	26	MCT	ORR: 50%, response to treatment predictive of survival	Hepatic, proteinuria, hematologic and GI, majority mild and self-limiting	Experimental, placebo-controlled trial	[169]
	Dogs	10	CEL	Overall clinical response: 70%	myelosuppression (mild), vomiting/diarrhea (grade 4 in 1 dog), grade 3 anorexia, petechiae, elevated ALT	Experimental, prospective clinical trial	[170]
	Dogs	39	MCT	Overall clinical response: 82.1%	Elevated ALT (grade 3 or 4), anemia (grade 3 or 4) and vomiting (mild) most common	Observational, retrospective	[171]
	Cats	20	—	N/A	proteinuria and neutropenia noted, increased serum Cr, and GI effects (mild)	Experimental, prospective, randomized phase 1 clinical trial	[172]

Xenogeneic Melanoma Vaccines

Combination	Species	N	Tumor Type(s)	Clinical Effects	Adverse Events	Study Type	Citation
Surgery, radiation, ± chemotherapy	Dog	9	Oral, nail/footpad, intraocular	MST: 389 d	Mild injection site reactions	Experimental, prospective (phase I); antigen: huTyr	[173]

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Table 2
(*continued*)

Xenogeneic Melanoma Vaccines

Combination	Species	N	Tumor Type(s)	Clinical Effects	Adverse Events	Study Type	Citation
Surgery, radiation, ± chemotherapy	Dog	170	Various	MST (stage II–IV): 389 d (huTyr), 153 (muGP75), 224 (muTyr)	Mild pain on injection	Experimental, prospective (phase I); antigens: huTry, muTyr, muGP75	[174]
Surgery alone ± steroids	Dog	111	Oral	Signficant improved survival over historical controls, MST could not be calculated	Mild injection site reactions, mild pain on injection	Experimental, prospective (phase II); antigen: huTyr	[175]
Amputation, radiation	Dog	58	Digit	MST: 476 d	Mild, local pain on injection, 9 dogs	Observational, retrospective; antigen: huTyr	[176]
Single agent or radiation	Dog	45	Oral	PFS (vaccinates): 199 d; (nonvaccinates): 247 d; no improvement in survival	Not discussed	Observational, retrospective; antigen: huTyr	[177]
Radiation, surgery	Dog	32	Oral	MST: 335 d	None observed	Observational, retrospective; antigen: huTyr	[178]
Surgical excision	Dog	38	Oral, digit, cutaneous	Oral: MST—26 mo; Digit: MST—36 mo; Other: 22 mo	None observed	Observational, retrospective; antigen: huTyr	[179]
Surgery, chemotherapy, radiation	Dog	11	Anal sac	MST: 107 d	None observed	Observational, retrospective; antigen: huTyr	[180]

Various chemotherapy, radiation	Dog	69	Oral	MST: 455 d	Not specified, stated as "minimal"	Observational, retrospective; antigen: huTyr	[181]
Various chemotherapy, radiation	Cat	24	Oral, ocular/ periorbital, dermal, mucocutaneous, lip, subcutaneous	Not evaluated	Minimal, grades 1 and 2 anorexia, nausea, 2 cats grades 3 and 4 myelosuppression	Observational, retrospective; antigen: huTyr	[182]
Radiation, surgical excision	Lion	1	Oral	Complete response	None observed	Case report; antigen: huTyr	[196]
Radiation, strontium	African penguin	1	Nare	14-mo survival (previous reported mean of 7 mo)	None reported	Case report; antigen: huTyr	[187]

Clinical benefit: complete response, partial response, or stable disease.

Objective response rate (ORR): complete response, partial response.

Abbreviations: AE, adverse events; ALT, alanine transferase; ASAGACA, anal sac apocrine gland adenocarcinoma; CCNU, Lomustine; CEL, canine epitheliotropic lymphoma; Cr, creatinine; CR, complete response; FISS, feline injection-site sarcoma; FOSCC, feline oral SCC; HNCA, head and neck carcinoma; HSA, hemangiosarcoma; IFN, interferon; LSA, lymphosarcoma; MCT, mast cell tumor; MCT, mast cell tumor; MH, malignant histiocytosis; MLO, multilobulated osteochrondrosarcoma; MMC, mixed mammary carcinoma; MST, median survival time; N/A, not reported; NCA, nasal carcinoma; OR, objective response; OS, overall survival; OSA, osteosarcoma; OSCC, Oral Squamous Cell Carcinoma; PCA, prostatic carcinoma; PFS, progression-free survival; PLN, protein-losing nephropathy; STS, soft tissue sarcoma; TC, thyroid carcinoma; Treg, regulatory T Cells; TTP, time to progression.

The second is masitinib (Masivet), targeting primarily the mutated forms of the c-kit receptor, platelet-derived growth factor receptor, lymphocyte-specific kinase, Lck/Yes-related protein, fibroblast growth factor 3, and focal adhesion kinase.[183] It is being researched in human oncology for the treatment of multiple cancer types (including GI stromal tumors, pancreatic tumors, and melanoma). Masitinib was approved for use in veterinary medicine for the treatment of nonresectable canine mast cell tumors and represented one of the only drugs approved for veterinary cancer patients that is also used in clinical trials for human patients. There are no published reports of masitinib use in exotics species. Masitinib, however, lost conditional approval from the Food and Drug Administration on December 15, 2015, and it is no longer legal for this drug to be distributed in the United States. It is still available, however, in the United Kingdom and other European countries, according to the European Medicines Agency, as of October 2017.[186]

Tumor Vaccines

In addition to the tyrosine kinase inhibitors described previously, there is a vaccine (Oncept; Merial, Duluth, Georgia) developed to target canine melanoma that has been reported in sporadic proceedings case reports in exotic species.[187,188] This is a xenogeneic (cross-species) vaccine that targets an enzyme, tyrosinase, that is expressed in melanoma cells. It is xenogeneic because it uses human tyrosinase to trigger an immune response to canine tyrosinase in canine patients. It is the only US Department of Agriculture–approved cancer vaccine approved for dogs. The treatment protocol for canine melanoma involves a transdermal vaccine every 2 weeks for 4 treatments and then vaccine boosters every 6 months. The evidence for improved progression-free survival in dogs treated with vaccines compared with traditional radiation and chemotherapy protocols is inconclusive and it is unclear at this time that there is a significant survival benefit for animals treated with this vaccine. Also, the expression of tyrosinase in canine melanomas can be variable according to published reports.[189] The value of this therapy for exotic species remains to be seen, and more studies are needed to determine its potential efficacy.

RADIATION THERAPY IN EXOTIC SPECIES

For patients with confirmed local disease where complete surgical resection is not possible due to anatomic or other considerations, radiation therapy is a reasonable therapeutic modality. The 2 major types of radiation are external beam and strontium 90, both of which have been reported in exotic species. When clinicians are considering radiation therapy, the authors strongly recommend consultation with a radiation oncologist because there are frequent improvements in radiation oncology relating to the ability to accurately map tumor tissue and spare normal tissue.[190]

External Beam Radiation

Two different types of external beam radiation can be distinguished—orthovoltage and megavoltage radiation therapy. Each has its own characteristics, which render them useable for different tumor types. Orthovoltage (x-rays of 150–500 kilovolt [peak]) has lower energy and, therefore, lower penetration, making it more appropriate for tumors of the skin and subcutaneous tissues. This type of radiation has a preference for bone and the chances of late effects (necrosis) on bony tissues is high. Megavoltage (photons >1 million MeV) is higher energy and effects build up in tissue. The interaction of megavoltage rays with tissue is more predictable and this radiation type is used in computerized radiation planning schemes. Advances in radiation planning software and machine hardware allow for more contoured radiation plans, sparing more normal tissue (**Fig. 7**).

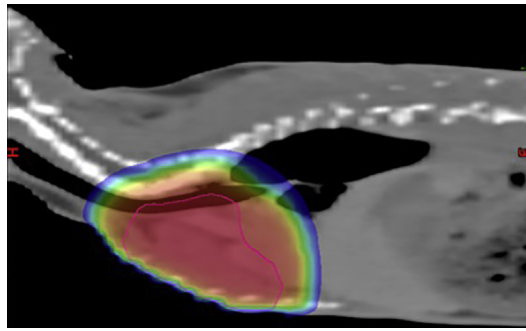

Fig. 7. Intensity-modulated radiation therapy planning in a rabbit for thymoma. (*Courtesy of* Tara Harrison, DVM, MPVM, Dipl. ACZM, Dipl. ACVPM, North Carolina State University.)

Tumors commonly treated with external beam radiation (in dogs and cats) include oral tumors, in particular melanoma and SCC, nasal tumors (sarcomas, carcinomas, and lymphomas), brain tumors, pituitary tumors, soft tissue sarcomas of the trunk and extremities, mast cell tumors, bone tumors (as part of multimodal therapy), and localized lymphomas. Recent reviews[14,21,191–193] have discussed the specific use of radiation in exotic species. Clinically, tumor types treated with radiation in exotics include a myxoma in a goldfish[191]; papilloma,[194] sarcoma,[195] and SCC[196] in reptiles; SCC,[197,198] melanoma,[199] hemangiosarcoma,[200] osteosarcoma,[201] lymphoma,[202] and fibrosarcoma in birds[203]; thymoma,[204] lymphoma, myeloma, seminoma, and nasal adenocarcinoma in rabbits[205–208]; preputial tumors[209]; chordoma[210]; SCC[211]; lymphoma[212]; and adenocarcinoma in ferrets.[213,214] In some cases, radiation can be used as a sole therapy, but it may also be combined with surgery or chemotherapy (in particular intralesional chemotherapy), depending on the tumor type/location and patient constraints (size and presence of comorbidities). Certain large tumors that cannot be resected may be treated with radiation to shrink them and make them more amenable to surgical resection. Also, radiation may be used after a surgical resection if the resection was determined to be incomplete on inspection of the margins.

Definitive versus palliative protocols

External beam radiation therapy can generally be broken into definitive and palliative protocols. The goal of definitive therapy is curative and involves an increased number of fractions and may provide higher gray/fraction. Definitive radiation is generally pursued if a patient is anticipated to live at least 1 year after therapy. These radiation protocols, however, may be associated with an increased risk of acute radiation side effects due to the increased number of fractions. Patients with an overall poor quality of life or a shorter life expectancy (generally <6 months) may be more appropriately treated with palliative protocols. These protocols have fewer fractions and have less frequent acute side effects.

Side effects and tolerance

The side effects of external beam radiation are divided into acute and chronic side effects. Acute side effects are related to the number of fractions provided as well as the area of the body being treated. Acute side effects may include mucositis, desquamation (dry or moist), and keratitis. Late radiation effects in mammals can include necrosis, fibrosis, nonhealing ulceration, central nervous system damage, and blindness, depending on the normal tissues being irradiated.[215] Although rare (1%–2% of cases) in humans and dogs, new tumors have been reported to develop at the site of radiation therapy. This has not yet been reported in avian oncology, but, given the long life span

of certain avian species, patients treated with radiation should be monitored for development of tumors at previous treatment sites.

The radiation tolerance of normal tissues in many species is not well defined and can be dramatically higher in some avian species. Quail and chickens are less radiosensitive compared with other animals, such as sheep, cattle, and swine, when whole-body irradiation effects on bone marrow are examined.[216–218] A study examined the tolerance dose of cutaneous and mucosal tissues in ring-necked parakeets (*Psittacula krameri*) for external beam megavoltage radiation and revealed minimal radiation-induced epidermal histologic changes in the high-dose group receiving 72 Gy in 4-Gy fractions.[219] A more recent study in macaws revealed that radiation delivered to the sinuses did not reach intended doses.[220] This implies that higher doses of radiation may be needed to produce equivalent response in avian patients compared with mammals, although the radiosensitivity of avian tumors has not yet been investigated. As in birds, studies examining the effects of radiation in other exotic species are mostly designed to effects of radiation contamination and not treatment efficacy.[14,21,191–193]

Strontium 90

Strontium 90 has specific indications for superficial tumors with less than 2 mm of depth. The level of radiation delivered decreases dramatically after 2 mm to 3 mm, so tumor staging is critical prior to choosing this modality. The circular area that can be treated with a strontium probe is approximately 8 mm and treated areas are arranged so they overlap to cover the entire tumor area. Common indications for strontium- 90 therapy include uropygial SCCs in birds, small tumors on the pinnal margin or nasal planum, and other superficial skin tumors as well as treating a tumor bed postexcision if there is concern regarding residual disease. Side effects of strontium 90 therapy are rare in the cases of it being been used and include local skin effects, such as alopecia, crusting, pruritus, leukotrichia, and thinning and depigmentation of the skin reported in cats.[221] Side effects in exotics have not been documented to the authors' knowledge.

OTHER/MISCELLANEOUS THERAPY TYPES

Hormonal/Steroidal Therapies

The most used hormones in veterinary medicine are corticosteroids, which are helpful in certain specific tumor types, including mast cell tumors, lymphomas, and lymphoid leukemias.[222] It is believed that steroids cause altered cellular transport of nutrients, apoptosis, and terminal differentiation in cancer cells. The effects are generally short lived, however, and there is concern of inducing multidrug resistance to chemotherapeutics in lymphoid cancers. Certain species are particularly susceptible to immunosuppression and secondary infection from the use of steroids, including birds and many small mammals, whereas others tolerate steroid therapy with few side effects (eg, ferrets). For steroid-sensitive species, prophylactic antibiotics and antifungals may be necessary when steroids are used as part of a cancer treatment protocol and patients should be closely monitored for signs of infection. Tamoxifen administration has not been evaluated for efficacy in cases of ovarian carcinoma, but antiestrogenic activity was suggested in 1 drug trial in budgerigars.[223] Gonadotropin-releasing hormone agonists (ie, leuprolide acetate) have been reportedly effective for ovarian carcinoma in birds in case reports in a small number of birds.[224,225]

Cryotherapy

Cryotherapy is reported infrequently in the exotic tumor literature.[132] It is a local therapy using extreme cold produced by liquid nitrogen or argon gas and is indicated in

treating small, local lesions or residual disease postsurgical resection. Repeated treatments may be needed to achieve tumor control[226] and patients should be monitored closely for recurrence. Treatment areas should be monitored for any related skin effects, but such side effects are rarely reported. Care should be taken if used over areas of bone because it can cause necrosis.

Other Types of Therapy

Other therapy types that have been reported in exotic species include phototherapy, hyperthermia, immunotherapy, nonsteroidal therapy, antiangiogenic agents, metronomic chemotherapy, electrochemotherapy, and complementary and alternative therapies, and these have been discussed in recent reviews.[13,20,227,228] Because they have been recently reviewed and there are only sparse data on efficacy of these therapies, they are not discussed in depth in this review. A brief review of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in anticancer therapies is provided.

Epidemiologic studies in man have demonstrated a protective effect of chronic aspirin intake in the incidence of colorectal cancer.[229] Anti-inflammatory drugs to slow or stop tumor growth have shown promise in several animal model systems and clinical cancer cases. A majority of NSAIDs inhibit the isoforms of cyclooxygenase (COX-1 and COX-2) or are selective for 1 isoform. The NSAID piroxicam has activity against a variety of tumors in humans and dogs. Piroxicam is used in the treatment of transitional cell carcinomas (TCCs) of the urinary bladder and urethra in dogs and has also shown benefit in treatment of some SCCs and mammary adenocarcinomas. Canine patients receiving piroxicam or meloxicam seem to have an improved quality of life, with increased activity and alertness reported by owners.[229] Oral piroxicam has uncommonly been associated with GI ulceration and renal papillary necrosis in dogs. Meloxicam or other selective COX-2 inhibitors may be safer alternatives to piroxicam in the treatment of cancer, because they may reduce possible GI side effects due to increased COX-2 selectivity, but their effectiveness as an anticancer therapy is less well studied.

TREATMENT STRATEGIES FOR TUMORS

Often, deciding on the appropriate treatment regimen for a particular patient with cancer can be bewildering. Some general principles remain unchanged, regardless of species, and some are highly species specific. No 1 book chapter or journal article can address every clinical situation and the authors strongly recommend close consultation with a boarded veterinary oncologist to make individual-level treatment decisions.

General considerations that apply to every cancer patient are the resectability of the primary tumor, the presence of multiple or distant lesions, technical or logistical concerns, and patient comorbidities. Exotic practitioners are limited by some additional concerns, because basic issues like obtaining repeated, dedicated venous access may not be possible. Exotic patients can be very small, and they generally require repeated anesthetic episodes for treatments like chemotherapy, which poses more of a risk than for dogs and cats, which do not require multiple anesthetic episodes. Additionally, many exotic species may hide underlying illnesses and may be more susceptible to immunosuppressive effects of corticosteroids, a commonly component of treatment of dogs and cats with certain lymphoid tumors. Clinicians need to work closely with owners to make sure they understand that nearly all the treatment recommendations the authors make for exotic patients are extrapolated from treatments

designed for human, dogs, or cats and there is only rare primary research examining the effectiveness of cancer therapy in exotic species. It is important to discuss with owners that necropsies at the time of death may provide additional information to expand the knowledge of behaviors of neoplasia in exotic species.

For every patient, the first question to ask of a diagnosed tumor is whether or not it is surgically resectable (Fig. 8). The first surgery represents the best chance of a cure and the surgeon needs to ask the following questions before planning a procedure: What is the histologic type and (to your best knowledge) the stage and grade of the cancer? What is the potential for local versus metastatic spread? Can a complete excision be performed and what are the cosmetic and functional trade-offs? and Are there any alternative options or plans for combined radiation or chemotherapy? This is the time when appropriate and interpretable diagnostics are key, to determine the true extent of the tumor and whether there is any evidence of distant disease because this would negate the reason for an extensive local surgical resection. Special considerations for exotic species include different healing capacities of skin types (mammal vs avian vs reptile) as well as elasticities for planning wound closures. Different species also tolerate different levels of surgical manipulations (eg, amputations) and knowledge of the normal anatomy and how well species can adapt to significant surgical alterations. Additionally, the planned "use" of the animal may guide therapy, in terms of whether this is a wild animal that needs to be released or a pet that can live with some level of disability.

For tumors where it is determined that surgical excision is feasible and indicated, basic oncological surgical principles apply. Appropriate surgical margins are not well defined for exotic species, and guidelines should be taken from histologically similar tumors in dogs, cats, or humans, where appropriate. The authors refer readers to recent excellent reviews on the topic and appropriate book chapters.[230,231] If surgical

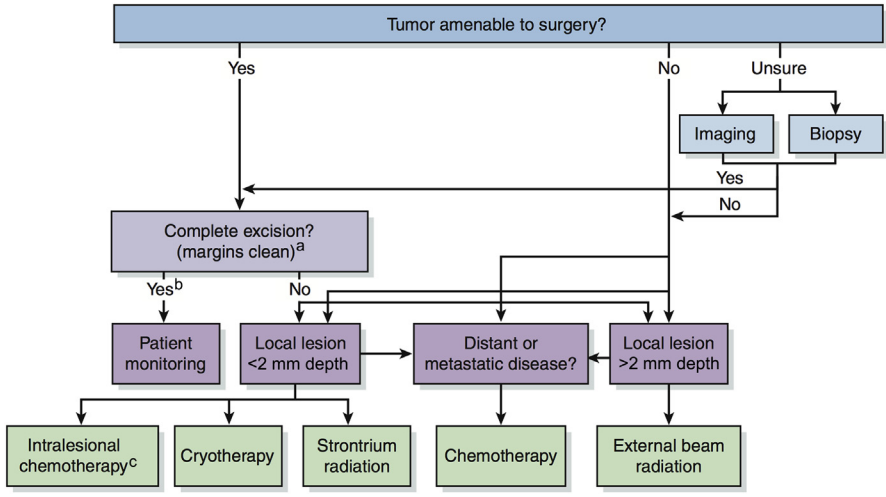

Fig. 8. Decision tree for exotic patients with neoplastic disease. [a] Recommended histology be performed on all excised tumors. [b] If tumor was high grade or there are metastases, adjunctive chemotherapy is indicated. [c] May be appropriate for lesions greater than 2 mm in depth depending on location and proximity to nearby vital structures. (*Adapted from* Zehnder A, Graham J, Reavill DR, et al. Neoplastic diseases in avian species. In: Speer B, editor. Current therapy in avian medicine and surgery. 1st edition. St Louis [MO]: Elsevier; 2016. p. 118; with permission.)

resection is not an option, if there is already distant disease detected, or if surgery is attempted but margins are not clean on histologic examination, additional therapies are determined by the lesion size, lesion depth, and presence of distant disease. For small local lesions or residual superficial tumor beds postsurgery, recommended treatments include intralesional chemotherapy, cryotherapy, or strontium 90 radiation. As discussed previously, strontium 90 is only important for lesions less than 2 mm in depth. For deeper but still local lesions, external beam radiation is considered more appropriate and the type and treatment protocol are guided by the histology. For distant lesions, chemotherapy or use of newer, molecularly targeted agents is appropriate. Again, the agent and protocol are guided by the type of disease as well as consultations with medical oncologists. The authors have attempted to discuss the indications for different chemotherapies as well as for newer molecular agents as a guide for clinicians. There is insufficient primary literature in exotic species, however, to be able to predict treatment efficacy or necessarily predict adverse events for specific patients, and owners need to be aware of these limitations.

NUTRITION/SUPPORTIVE CARE FOR EXOTIC CANCER PATIENTS

Appropriate nutritional support is vital for cancer patients. Cancer cachexia (CC) is a well-known phenomenon that has been described in both human and veterinary species.[232] CC causes significant changes in nutrient metabolism, leading to weight loss and muscle atrophy. CC is typically progressive and can have a significant impact on both length and quality of life if it is not appropriately managed.[233] Although no studies have been published on whether CC occurs in avian and reptile species, it is probable that they experience a similar syndrome, because progression of neoplasia in exotic species usually closely mirrors progression in other species.

Recommendations for management of CC include feeding a highly digestible diet that is limited in simple carbohydrates, contains moderate amounts of highly bioavailable amino acids, and contains increased amounts of fat. Supplementing the diet with omega-3 polyunsaturated fatty acids, eicosapentaenoic acid and docosahexaenoic acid, may be protective against some of the common metabolic abnormalities associated with CC and may improve response to treatment.[234] Omega-3 polyunsaturated fatty acids can be generally recommended as a healthy supplement for avian and other exotic patients, because they are also beneficial for cardiovascular, skeletal, and neurologic health.[235] Adequate insoluble fiber intake can improve GI health and promote normal GI flora, which may benefit patients undergoing cancer therapy.[236]

Unfortunately, there is no published information on the association of different dietary factors with cancer in exotic species. The impact of vitamins, minerals, and micronutrients on cancer risk and treatment has been extensively discussed in the human literature.[237] Carotenoids, selenium, folic acid, and vitamins A, C, E, and D have all been linked in certain studies to a reduction in cancer risk; however, many studies have produced conflicting information, and there is currently limited consensus on their correlation to cancer development.[238]

Regardless of which dietary supplements are elected for use in a cancer patient (if any), the patient must eat to benefit from nutritional support. The use of appetite stimulants, such as vitamin B complex or benzodiazepines, may be helpful.[239–241] Warming the food prior to offering it to a patient and decreasing stress in the surrounding environment may improve food acceptance. Appropriate medical management of pain and nausea is an extremely important factor. Metoclopramide may be used to help decrease nausea, improve appetite, and improve normal GI motility.[242] The efficacy and safety of other antinausea medications have not been critically evaluated in birds and other exotic species.

If necessary, supplemental gavage feeding or placement of an esophagostomy/ingluviotomy tube can be performed for long-term nutritional management. There are a variety of commercially available liquid critical care diets for exotic species that can be used for nutritional supplementation via these methods.

PATIENT MONITORING AND SIDE EFFECTS

In exotic animal practice, there is a lack of standardization for quantifying patient outcomes as well as adverse effects. This lack of consistency and quantitative patient information greatly hinders the ability to combine cases from different institutions as well as to assemble larger case series to analyze population-level data for different types of cancers. Within canine and feline oncology, as well as within human oncology, there are extensive tools for this type of patient monitoring and these should be adapted, as appropriate, for exotic patients. It is crucial for clinicians to convey to owners the importance of regular rechecks, even when patients are apparently doing well, and to inform veterinarians when patients die at home. Owners should be encouraged to allow necropsy whenever feasible, because it may be hard to know otherwise if therapies are truly effective or if there are subclinical side effects from therapy that may not otherwise be diagnosed.

Adverse Events

There is a range of adverse events that may occur secondary to chemotherapy administration, radiation treatment, or other cancer therapies. For patients undergoing chemotherapy, CBCs should be monitored weekly to biweekly, and treatment should be delayed if the heterophil/neutrophil count is too low. Based on information obtained in dogs and cats,[119,243] it is recommended that treatment should be delayed in patients with a heterophil (in birds and reptiles) or neutrophil (in mammals) counts less than 2000 cells/μL if a drug that is generally considered myelosuppressive is scheduled. If the drug is not considered myelosuppressive, it may be possible to administer therapy as long as the heterophil/neutrophil count is 1500 cells/μL. A conservative rule is to administer appropriate antimicrobial therapy to any avian or exotic patients with a heterophil count below 2000 cells/μL or less than 25% of the normal reference range for the species in question.

The Veterinary Cooperative Oncology Group (VCOG) has established common terminology criteria for adverse events after chemotherapy or biological antineoplastic therapy in dogs and cats.[184] These documents define an adverse event as “any unfavorable and unintended sign, clinical sign, or disease temporally associated with the use of a medical treatment that may or may not be considered related to the medical treatment.” Adverse events are categorized by different body systems with a separate category for clinical pathology. There is a grading scale that quantifies the severity of the observed effects. Generally, grade 1 is mild and may be subclinical, grade 2 is moderate, grade 3 is severe, grade 4 is life-threatening, and grade 5 is death. Adverse events in exotic species being treated for cancer should be recorded and can be based on this information. A modified table for avian species is published in the recent review of avian oncology by 2 of the authors and the same authors are developing a more general version appropriate for additional exotic species.[13] It is important for clinicians to understand that they do not necessarily need to work out if the adverse event is a direct consequence of a treatment. For patients treated with combinations of therapies, it may not be clear which treatment is responsible for an observed event or an event may be due to an underlying disease process. It is important, however, to record any adverse events that are noted and make it clear in the medical record the

doses, dosing intervals, and periods of time when treatments are administered so that cases can be accurately analyzed retrospectively for potential adverse events.

Assessing Response to Therapy

Human oncologists use Response Evaluation Criteria in Solid Tumors (RECIST) to objectively monitor primary tumors (target lesions) and lymph nodes and provide a standardized way to compare outcomes across multiple clinical trials and patient populations. These criteria received a major update in 2009 and are used in a majority of clinical trials.[244] The VCOG published an adapted version of these criteria for canine solid tumors in 2015.[245] Even in dog and cat oncology, these standards are not well established. There are a few basic guidelines, however, that clinicians can adopt into their practice to make their patient assessments more quantitative and allow accurate patient assessments over time.

Basic RECIST guidelines address the following points: baseline tumor measurements, methods of tumor assessments, evaluation of tumor response, and definitions of progression-free survival. Accurate, baseline tumor assessments (**Fig. 9**) are the key to objectively evaluating a patient's later response to therapy. It is recommended that measurements be taken as close as possible to the initiation of therapy. Lesions that are larger than 10 mm should be followed either with caliper measurements (for cutaneous lesions) or imaging modalities for internal lesions (where feasible). Ultrasonography is not recommended for repeated tumor assessments if other options are available. Due to the imprecise nature of radiographs and ultrasound, only lesions greater than 20 mm should be routinely monitored using these modalities. If patients have PET scans, they can be used to monitor response but not for accurate lesion measurements. Consistency is also important when tracking lesions. If caliper measurements are used, it is advisable for the same people to obtain those measurements at subsequent visits. CT scans are preferred over radiographs; however, these are not always feasible due to concerns over cost and longer anesthesia times. If ultrasound scans are used to follow lesions, it is important to use the same radiologist for the scans and use previous images to guide acquisition of new images so they are obtained in the same plane. In evaluation of patient response, clinicians should attempt to quantitate a patient's overall tumor burden in all measurable lesions. The longest diameters of target lesions (those that are measured repeatedly over time) are summed to obtain the "baseline sum diameters." This is the reference for assessing patient response.

Fig. 9. Using calipers to measures a patagial SCC in a cockatiel prior to chemotherapy administration.

There are 4 different potential patient outcomes to any cancer treatment: complete response, partial response, progressive disease, and stable disease. Complete response describes the complete disappearance of all target (measured) lesions. Partial response describes at least a 30% reduction in the sum of diameters of target lesions (using the baseline sum as a reference). Progressive disease describes the appearance of new lesions or a 20% or greater increase in the sum of diameters of target lesions. Stable disease describes less than 30% decrease or less than 20% increase in tumor burden. There are additional details regarding nontarget or nonmeasurable lesions and the authors suggest reading the VCOG consensus document for more information.[245]

FUTURE DIRECTIONS

A recurring theme in every article and book chapter relating to cancer therapeutics in exotic and zoologic species is the extreme lack of remotely sufficient published knowledge regarding basic tenets of cancer biology and treatment of these species. Clinicians and researchers often are essentially guessing at the best therapies from 1, 2, or, in some cases, no published reports and every patient is an n of 1, particularly for more rare tumors in rarer species. The questions that remain to be asked are many. Do histologically similar tumors in these species behave like their counterparts in humans, dogs, or cats? Are the underlying genetic or molecular alterations similar and how do they affect patient prognosis? How long will a certain animal live with a particular tumor without treatments and which treatments actually prolong life? How do clinicians and researchers appropriately extrapolate therapies across species with widely different metabolisms, different dose tolerances, and potential species-specific toxicities? How can the level of case documentation, tumor quantification. and outcome and side effects reporting be improved to be able to better integrate clinical cases with those from other species?

How to do this is by better communicating cases to others and by accumulating cases in a central location with standardized clinical information, to start drawing statistically valid conclusions from clinical data. The Exotic Species Cancer Research Alliance is one such effort and has built a repository for clinical cases (Exotic Tumor Database) to try to answer some of these questions. Information regarding this effort is at www.escra.org, where there are resources to help clinicians find and enter their cases for the collective good of exotic clinicians and their patients.

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