CHAPTER

28

Oncology

OUTLINE

BASIC APPROACH TO THE FELINE CANCER PATIENT

Brooke Fowler

SIGNS OF CANCER

All too commonly, the veterinarian sees a feline patient after clinical signs have exceeded the client's perception of health. Subtle behavioral changes may occur long before overt clinical signs appear. These changes vary depending on the type of malignancy and which body systems are most affected. General changes in activity, appetite, and litter box use are perhaps the most common first indications that a disease process is under way (see Box 37-3).

SCREENING DIAGNOSTICS

General health screening is the first step for the ill cat or a cat whose clinical signs designate the location of the disease. A complete blood count (CBC) can reveal hematologic malignancies and bone marrow–infiltrating diseases. The CBC is also an excellent way to primitively assess the innate immune system. Biochemistry data aid in the evaluation of general organ function as well as screening for hepatic lipidosis, the most common secondary disease.[1] General body cavity imaging is necessary because not all malignancies lead to biochemical alterations. Complete staging generally includes both abdominal and thoracic radiographs and potentially abdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI).

GENERAL STAGING TECHNIQUES

Each cancer type has its own predilection for sites of metastasis, and therefore staging is tailored to individual type. However, general assumptions can be made. By knowing the cell type of origin, the veterinarian can predict the route by which cancer will metastasize. Round cell tumors tend to metastasize by way of the lymphatics. Therefore examination of the draining lymph nodes surrounding round cell tumors is part of any thorough cancer workup. Mesenchymal cell tumors tend to metastasize hematogenously. Therefore thoracic radiographs are always indicated. Lastly, epithelial tumors tend to metastasize by way of either lymphatics or blood. Lymph node imaging and aspiration, as well as thoracic radiographs, are warranted to assess the metastatic status of a patient with a carcinoma. Aberrant metastatic patterns can suggest aggressive behavior. Sarcomas spreading by lymphatics or round cell tumors metastatic to pulmonary parenchyma may suggest a worse-than-typical prognosis for that patient. CT scans and MRI can be used to diagnose disease in closed cavities such as the skull, spine, and thoracic cavity. CT and MRI scans can be used to better plan for surgery. Another commonly used diagnostic modality is nuclear scintigraphy. Radioactive isotopes can be tagged to target certain body tissues. These radioisotopes can be used to locate bony lysis or even to elucidate the biological activity of a thyroid mass.

Fine-Needle Aspiration and Cytology

Most palpable masses can be aspirated with a needle. Fine-needle aspiration is the least invasive diagnostic approach that still offers high yield to define the malignancy.

Technique

The veterinarian should use the smallest needle necessary to safely and adequately collect cells for diagnosis. Needles of 22 to 25 gauge are typically sufficient, even for masses present in bone. Two methods exist for a fine-needle aspirate. The first method uses a needle without an attached syringe or with a syringe containing 6 mL of air. In an oscillating motion, the clinician inserts the needle into the lesion multiple times to collect sufficient cells for a smear. Using 6 mL of air, the clinician forcefully expels the contents of the needle onto a slide. The expelled material is gently spread on a blank slide to create a monolayer of cells. One slide is stained to ensure that cells were obtained and adequately prepared. The rest of the sample is sent unstained to a clinical pathologist. The second technique involves placing the needle into the lesion and aspirating with the syringe. The clinician removes the needle, fills the syringe with 6 mL of air, reattaches the needle, and then forcefully expels the contents of the needle onto a slide and prepares as previously described.

Advantages

Fine-needle aspiration is minimally invasive and rarely requires sedation or anesthesia. A diagnosis often can be made rapidly and at little cost to the patient and the client. This technique can be performed for skin, bone, and internal organ lesions.

Disadvantages

This approach collects a small sample that is assumed to be representative of the entire tumor population. The heterogenous nature of tumors with varied oxygenation and inflammatory components can confound this assumption. This test may yield nondiagnostic results and delay the diagnosis. Cytologic diagnosis often depends on the type of tumor. Round and epithelial cells may exfoliate more completely than tumors of mesenchymal origin.

BIOPSY TECHNIQUES

Biopsy samples should be taken along the periphery of a lesion, as a general rule. This will ensure that the necrotic center of a mass will not be sampled instead of the viable portion. This also facilitates skin closure. Neoplastic tissue has poor healing capabilities. The one exception to this rule is a tumor of bone. When a biopsy of bony tumors is performed, the track should include the center of the lesion. Aspirates or biopsies performed at the periphery of a bone lesion will likely yield reactive bone.

Punch Biopsy and Needle Biopsy

Punch biopsy and needle biopsy are the least invasive of the biopsy techniques. A punch biopsy is more suitable for external skin lesions. A Tru-Cut biopsy is more suitable for sampling internal organ lesions with imaging guidance.

Technique

When a biopsy punch is used, cutaneous and subcutaneous samples can be acquired transdermally or through a small skin incision. The biopsy punch is twisted, always in the same direction, into the lesion to the desired depth within the mass. With Metzenbaum scissors the sample is cut away from adherent underlying tissues. The sample is placed in formalin at a ratio of 1:10 (tumor:formalin) and submitted to a pathologist, who will provide a complete microscopic description, diagnosis, grade, margin description, and mitotic index as indicated. For a needle biopsy, a Tru-Cut biopsy

needle is required. A Tru-Cut biopsy requires a special tool. This needle biopsy tool is inserted into the lesion. The core of the needle biopsy device is extended into the tissue mass. The sheath of the needle biopsy device is then advanced, and a portion of tissue is cut free within the notch of the core. Multiple specimens should be collected. Automatic firing devices can speed the collection of each sample. However, these automated, spring-loaded devices can be too vigorous for internal organs, causing organ damage in smaller patients.[3]

Advantages

These techniques require either a short anesthetic experience or sedation and a local block. These techniques require minimal surgical closure, resulting in less risk of dehiscence or infection compared with a major surgery. These techniques may allow a pathologist to identify the neoplastic process with description of the tumor's architecture. These samples may also allow for immunohistochemical stains and further prediction of the biological behavior of the tumor.

Disadvantages

These procedures may result in a nondiagnostic sample. Crush artifact is a common occurrence with these techniques. Surgical dehiscence is also a potential complication, as well as the aforementioned risk of organ damage associated with automated devices.

Wedge Biopsy

Removing a small but representative sample of the tumor facilitates identification of tissue architecture, allowing the pathologist to make a diagnosis and identify potential lymphatic or vascular invasion. A wedge of tissue is incised into the lesion along the edges. This wedge should have the smallest side along the center of the lesion and the longest side along the lateral margins.

Advantages

This technique allows a larger sample to be obtained. Sample architecture can be examined by a pathologist. Further information may be gained, including biological behavior and immunohistochemical staining. Because the portion of tissue that is being sampled is larger, the likelihood of obtaining a diagnosis is higher.

Disadvantages

This technique involves general anesthesia and all its associated risks. This procedure also carries a greater risk of dehiscence. Tumors do not heal as well as normal tissue does. This procedure carries some risk of spreading the tumor within normal tissue and requires careful planning to keep cells and hemorrhage contained within the ideal excisional surgical field.

Excisional Biopsy

Complete excision of the tumor can be at once diagnostic and therapeutic. Failure of complete excision functionally spreads the tumor farther inside the patient, potentially worsening the prognosis.[2]

Technique

Excision of a mass should be attempted only with careful prior planning to ensure a complete excision. Lateral margins must be at least 2 to 3 cm wide, and one complete fascial plane must be resected deep to the mass for the excision to be considered complete. Given the small size of the feline patient, this may not be feasible. Such margins can be particularly difficult to achieve with injection-site sarcomas, making preoperative imaging necessary for surgical planning. If complete excision is not considered highly likely, the veterinarian should consider an incisional biopsy for diagnosis before a major surgical procedure.

Advantages

This technique provides a potentially curative sampling diagnostic.

Disadvantages

This is the most aggressive biopsy technique. It may not be advisable if the surgery is a potential threat to patient function. This technique also requires general anesthesia.

References

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2. Hershey AE, Sorenmo KU, Hendrick MJ et al: Prognosis for presumed feline vaccine-associated sarcoma after excision: 61 cases (1986-1996), *J Am Vet Med Assoc* 216: 58-61, 2000.
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CHEMOTHERAPY FOR THE FELINE CANCER PATIENT

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Chemotherapy is primarily effective against tumors of minimal bulk with a high mitotic proportion. Some cancers, such as lymphoma, are treated primarily with chemotherapy. For other tumor types, chemotherapy is used in an adjuvant setting after radiation therapy or surgery (or both) or a neoadjuvant setting before radiation or surgery (or both). Treating cats with chemotherapy is no more technically challenging than many veterinary procedures. However, the decision to administer chemotherapy must include an assessment of risk

to staff and cats that is unique to this modality, as well as the expense and practicalities of safely storing, preparing, and administering chemotherapeutic agents.

Treating cancer in cats is similar to managing any chronic disease in this species; the veterinarian's goals should be to treat the underlying disease while maintaining or improving the pet's quality of life throughout treatment. To ensure that chemotherapy is both safe and appropriate for the cat, an accurate cytologic or histologic diagnosis must be reached, and any concurrent health problems must be identified to assess the risk of toxicity to the individual cat. Staging tests, such as CBC, serum chemistry profile, urinalysis, thoracic radiographs, abdominal ultrasound, CT scan, MRI, and bone marrow aspirate cytology, are often needed to determine if the cancer is localized to one area or if it has metastasized. Advanced-stage cancers generally carry a poorer prognosis and increased risk of toxicosis as a result of treatment. This may alter the owner's willingness to pursue treatment. The owner should understand the expected prognosis for the cat as well as the possible risks, cost, and time commitment associated with therapy.

The aim of this section is to provide information regarding the safe handling and administration of chemotherapy as well as information regarding dosing and potential toxicoses of some of the chemotherapy agents commonly administered to cats. Additional resources are found in Box 28-1.

BOX 28-1

Additional Resources

ASHP guidelines on handling hazardous drugs, *Am J Health Syst Pharm* 63:1172-1191, 2006. http://www.ashp.org/DocLibrary/BestPractices/PrepGdlHazDrugs.aspx.

Burroughs GE, Connor TH, McDiarmid MA et al: Preventing occupational exposure to antineoplastic and other hazardous drugs in health care settings, National Institute for Occupational Safety and Health, 2004. http://www.cdc.gov/niosh/docs/2004-165/.

Chemotherapy and managing oncologic emergencies. In Henry CJ, Higginbotham ML: *Cancer management in small animal practice,* St. Louis, 2010, Saunders Elsevier, pp 101-135.

Chun R, Garrett LD, Vail DM: Cancer chemotherapy. In Withrow SJ, Vail DM: *Withrow and MacEwen's small animal clinical oncology*, ed 4, St. Louis, 2007, Saunders Elsevier, pp 163-192.

Thamm DH, Vail DM: Aftershocks of cancer chemotherapy: managing adverse effects, *J Am Anim Hosp Assoc* 43:1, 2007.

CHEMOTHERAPY PREPARATION

The risk of exposure of personnel to chemotherapy drugs is greatest during preparation and administration. These cytotoxic drugs may have mutagenic and carcinogenic effects. All staff members should be aware of the risks of exposure to these drugs and follow protocols to minimize these risks. Clinics that administer chemotherapy should have a written set of guidelines for the safe handling of chemotherapy drugs and plans for managing chemotherapy spills or other exposures.[1,6] Areas where chemotherapy is prepared and administered should be clearly marked, and traffic through those areas should be limited. Storage or consumption of food and beverages, including gum chewing, should be prohibited in these areas to prevent accidental ingestion. Cytotoxic drugs should be stored separately from other medications and their location clearly identified.

Facilities where injectable chemotherapy agents are prepared ideally should have a class II biologic safety cabinet that is vented to the outside and located in a space designated for chemotherapy preparation. The area should be free of clutter, and workroom surfaces should be disinfected with bleach. The work surface should be covered with an absorbent pad with a nonporous backing to help contain any spills that do occur. Compounding pharmacies can be used to prepare drugs for administration if space and proper equipment are cost prohibitive for the clinic. Items required for preparation of antineoplastic drugs are listed in Box 28-2. Personal protective equipment (PPE), including gloves, gown, protective eyewear, shoe covers, and a respirator or heavy-duty mask, should be worn when preparing cytotoxic drugs. Gowns should be made of a low-permeability fabric and have a closed front and long sleeves with elastic cuffs. Chemotherapy gloves or two pairs of latex, nitrile, or neoprene gloves are recommended, and gloves should be worn over the cuffs of the gown. Powder-free gloves should be used because the powder may absorb contaminants and increase the risk of exposure. A chemotherapy spill kit should be easily accessible in all areas where chemotherapy is handled. Box 28-3 lists the items necessary for a chemotherapy spill kit; alternatively, ready-made spill kits can also be purchased.

Reconstitution of chemotherapy drugs may cause aerosolization of the agent. For this reason devices designed to prevent aerosolization should be used. Chemotherapy dispensing pins are venting devices with a 0.22-micron filter that reduce pressure in the chemotherapy vial when reconstituting and dispensing chemotherapy drugs, thereby decreasing the risk of spraying or spillage. Optimally, a closed-system drug delivery device such as PhaSeal (Carmel Pharma, Columbus, Ohio) or a contained medication system such as

BOX 28-2
Requirements for Chemotherapy Preparation and Administration

Chemotherapy Preparation

- Personal protective equipment
- Absorbent pad with nonporous backing to cover preparation surface
- Needles, Luer-Lok syringes, syringe caps
- Drug-containment devices such as PhaSeal or ONGUARD
- Appropriate diluent, as indicated on the drug package insert
- Sealable plastic bag for transporting chemotherapy
- Hazardous waste container
- Dedicated chemotherapy sharps container
- Labels

Chemotherapy Administration

- Personal protective equipment
- Properly labeled chemotherapy drug
- Disposable, absorbent pad with nonporous backing
- Catheter setup: Surgical prep, butterfly or over-the-needle catheter, tape, T-port adapter
- PhaSeal adapter (if appropriate)
- Two syringes of nonheparinized saline flush
- Bandage for catheter site (after removal)

BOX 28-3
Chemotherapy Spill Kit Requirements

- Two pairs powder-free latex or nitrile gloves or chemotherapy gloves
- Disposable closed-front gown with elastic cuffs
- Disposable shoe covers
- Protective eyewear
- Respirator or heavy-duty mask
- Absorbable pads (disposable diapers, Chemosorb pad)
- Several large, sealable plastic bags for chemo waste

BOX 28-4
Suppliers of Chemotherapy Safety Equipment

Biological Safety Cabinets

- Esco Technologies
- NuAire Laboratory Equipment Supply
- Terra Universal
- Thermo Fisher Scientific

Chemotherapy Delivery Devices

- Chemotherapy dispensing pins
  - B Braun Medical
  - Specialty Medical Group
- PhaSeal; Carmel Pharma
- ONGUARD; B Braun Medical

ONGUARD (B Braun, Bethlehem, Penn.) can be used. Closed-system devices prevent aerosolization of drugs and provide leak-free (dry) connection between the vial, syringe, infusion set, and the cat; they have been demonstrated to decrease surface contamination and personnel exposure.[43,44] Regardless of the venting or delivery device used, the use of Luer-Lok syringes is essential when reconstituting or drawing up chemotherapy drugs to prevent accidental disconnection of the syringe from the delivery system. Intravenous fluid lines should be primed before the addition of the chemotherapy agent to the infusion bag to prevent contamination when priming the line. Once chemotherapy preparation is complete, the drug should be placed in a sealable plastic bag for transport to the administration area to contain any leaks or spills that may occur during transportation. Suppliers of chemotherapy equipment are listed in Box 28-4.

All materials that have been in contact with chemotherapy agents during preparation and administration should be disposed of in a designated chemotherapy waste container. This includes gloves, gowns, absorbent pads, catheter materials, syringes, fluid bags, and intravenous lines that that have been used for chemotherapy administration. Sharps should be disposed of in a designated chemotherapy sharps container. To prevent accidental inoculation, needles should never be recapped. Waste that has been identified as chemotherapy waste should be handled separately from other hospital waste. Regulations regarding proper disposal of hazardous waste vary among municipalities; local and state officials should be consulted to ensure that disposal meets with Environmental Protection Agency standards in the United States and with the standards of the respective authorities in other countries.

CHEMOTHERAPY DOSING AND ADMINISTRATION

Obtaining a thorough history at each visit will help the practitioner identify any toxicosis that the cat may have experienced during prior chemotherapy, as well as guide treatment delays and dose reductions if the owner decides that the cat's quality of life is adversely affected by treatment. At each appointment cats should have their body weight, temperature, heart rate, and respiratory rate recorded and receive a complete physical examination. A CBC should be performed before each

dose of chemotherapy. A biochemical panel should be performed as needed depending on the toxicity profile of the drug to be administered. Cats that appear to be feeling unwell at the time of the chemotherapy appointment should not be administered chemotherapy that day, and appropriate diagnostic tests should be performed to identify any new problems or complications from therapy. If the cat is determined to be ill secondary to its cancer, it should be treated with the goal of obtaining remission and improving the cat's quality of life.

The cat's chemotherapy dose should be calculated from the current body weight. The clinician should pay particular attention to whether the drug is to be dosed on the basis of body weight (kilograms) or body surface area (m^2). A chart converting body weight into body surface area should be easily accessible when calculating the chemotherapy dose. A system by which a second person double-checks drug type, dosage, and calculation of dose is important to prevent dosing errors. The cat's name, drug type, and drug dose should be double-checked again against the label on the drug, the patient chart, and patient identification tag or collar before administration to ensure that the cat receives the correct type and amount of drug. Additionally, a record documenting the drug given, dose and route administered, vein used for chemotherapy administration, initials of person administering the drug, and any adverse reactions should be maintained in the cat's chart. The various routes of chemotherapy administration are discussed in greater detail in subsequent sections.

Personnel should be instructed in the proper handling and disposal of waste from chemotherapy patients. Owners should be given written instructions regarding these as well. Depending on the drug administered, urine, feces, saliva, and vomitus may contain small amounts of chemotherapy agents and their metabolites for as long as 72 hours after administration; chemotherapy drugs that undergo substantial protein binding may not be fully excreted for as long as 21 days after treatment.[26] While the cat is in the hospital, cage cards identifying chemotherapy patients should be used to alert staff members responsible for cleaning soiled cages. Soiled linens should be washed separately, and disposable gloves should be worn when cleaning up urine, feces, or vomitus during this time. Litter boxes should be changed daily for several days after treatment, and use of litter-box liners may help prevent aerosolizing chemotherapy metabolites. Cats in multicat households do not need to be separated because there is no reported risk associated with sharing litter boxes or food dishes.

Oral Administration

Numerous oral antineoplastic drugs are commonly used in veterinary oncology. Although these are often perceived by pet owners to be safer and easier to administer than intravenous agents, clients must be counseled regarding the proper handling of these medications. Tablets should never be split or crushed, and capsules should not be opened; doing so may lead to the owner's exposure through inhalation, skin contact, or ingestion. Similarly, liquid medications should never be compounded. Owners should be given disposable, latex, powder-free gloves to wear when handling oral chemotherapy agents, and hands should be washed after administration. Cats should be encouraged to eat a small amount of food or carefully syringed several milliliters of water after administration of the drug to ensure passage of the tablet or capsule into the stomach. Some owners will request that the oral chemotherapy agent be administered while the pet is at the hospital. This can be problematic if the cat is prone to motion sickness and vomits the medication during the car ride home. If the owner is capable, administration of the drug once the pet is at home is preferable.

Intravenous Administration

It is recommended that the jugular veins be used for blood collection to preserve peripheral veins for chemotherapy administration. An atraumatically placed indwelling intravenous catheter should be used for administration of chemotherapy volumes greater than several milliliters. This step is critical in prevention of extravasation because many chemotherapy drugs are potent vesicants. If the catheter is not placed cleanly on the first attempt, the clinician should remove the catheter and attempt placement in a different peripheral vein. Sedation should be considered for fractious cats to ensure that the intravenous catheter remains in place throughout infusion of the chemotherapy agent. If possible, the catheter site should not be bandaged to allow the clinician to observe any signs of extravasation during administration.

Box 28-2 lists the equipment necessary for intravenous administration of cytotoxic drugs. PPE, as previously described, should be worn by the individual administering the drug and any personnel involved in restraint of the cat. An absorbent pad with a plastic backing should be placed underneath the limb into which the drug is to be delivered. A butterfly catheter can be used for cooperative cats receiving small chemotherapy volumes (<3 mL). For larger volumes an indwelling catheter should be placed and the cat closely monitored throughout the infusion. The catheter should be flushed thoroughly with nonheparinized saline before administration to ensure its patency. Chemotherapy agents should not be infused with an intravenous fluid pump. Chemotherapy drugs should be administered by slow gravity drip or manual syringe infusion over the recommended time of administration. The fluid bag should be lowered beneath the cat every few minutes to

ensure that blood is able to flow back in the catheter. If the drug is administered through a syringe, the plunger should be aspirated back several times during administration of the drug to ensure that blood still appears in the hub of the catheter. The catheter site should be monitored throughout administration and administration discontinued if any swelling at the catheter site is observed. Once the chemotherapy infusion is complete, the catheter should be flushed again with nonheparinized saline before removal. A light bandage should be placed over the catheter site after removal.

Intramuscular, Subcutaneous, and Intralesional Administration

Intramuscular or subcutaneous injections are administered in the same manner as any other intramuscular or subcutaneous injection, but disposable gloves should always be worn. Because L-asparaginase is more likely to cause an anaphylactic reaction when administered intravenously, aspiration of the syringe should be performed before intramuscular or subcutaneous administration to ensure that a blood vessel has not been inadvertently entered. Chemotherapy drugs that are administered intralesionally are always suspended in oil or another vehicle to help prevent the drug from leaking out of the tumor tissues into the bloodstream. Disposable gloves and a protective gown and eyewear should be worn during administration, and a disposable, absorbent pad should be placed underneath the part of the body to receive the intralesional chemotherapy. All materials used in intramuscular, subcutaneous, or intralesional chemotherapy administration should be disposed of in the same manner as for intravenous administration. Urinary and fecal waste should be handled as previously described in the hospital and at home after intralesional injection.

Intracavitary Administration

Chemotherapy agents such as carboplatin and mitoxantrone may be administered in the pleural or peritoneal space to mitigate malignant effusions. The intracavitary dose of chemotherapy is generally the same as that administered intravenously and can be administered into a single body cavity or divided between the thorax and the abdomen. The chemotherapy drug should be diluted with the appropriate diluent to a maximal volume of 60 mL for intrathoracic administration and 250 mL for intraabdominal administration.[34] As appropriate, effusions should be drained from the cavity before instillation of the chemotherapy agent.

For intrathoracic chemotherapy administration, the cat can be positioned in sternal or lateral recumbency and the thoracic wall overlying the seventh to ninth ribs aseptically prepared. Proper PPE should be worn in a similar fashion as for intravenous administration. An 18-gauge catheter is then inserted between the ribs, the stylet removed, and the catheter flushed with 2 to 5 mL of warmed saline to ensure patency. If the cat is uncomfortable or begins to cough, or the catheter does not flush easily, the catheter should be removed and a new one inserted. If the cat tolerates the flush well, the drug can then be administered while the catheter site is monitored continuously to ensure that the drug is not inadvertently administered subcutaneously. The catheter insertion site can be blocked with a small amount of buffered lidocaine before the procedure to minimize discomfort.

For intraperitoneal administration the cat should be placed in dorsal recumbency, and a site on the abdomen just caudal to the umbilicus should be aseptically prepared. The urinary bladder should be identified with palpation to prevent accidental puncture. The 18-gauge catheter can then be placed and the chemotherapy administered as previously described. After administration of intracavitary chemotherapy, some authorities recommend allowing the cat to move around for several minutes to ensure distribution of the drug throughout the body cavity.

GENERAL ADVERSE EFFECTS OF CHEMOTHERAPY

Gastrointestinal

Chemotherapy agents can be directly cytotoxic to the intestinal epithelial crypt cells resulting in gastrointestinal side effects about 2 to 5 days after administration. Less commonly, some chemotherapy agents may cause release of 5-HT from enterochromaffin cells in the gastrointestinal tract, which binds to 5-HT_3 receptors on peripherally vagal nerves or centrally in the chemoreceptor trigger zone. 5-HT_3–mediated nausea and vomiting tend to occur within 24 hours of chemotherapy administration. These side effects may include mild to severe inappetence, nausea, vomiting, and diarrhea. For the majority of cats, gastrointestinal side effects secondary to chemotherapy are mild and self-limiting and often can be easily managed by owners at home with the administration of oral antinausea and antidiarrheal drugs on an as-needed basis. Oral antiemetics such as metoclopramide, ondansetron, and maropitant (see Table 28-5) can be dispensed at the time of the first chemotherapy appointment, whereupon owners should be instructed when to give the medications. Medications such as tylosin and metronidazole can be dispensed in a similar manner for owners to administer in the case of soft stools or diarrhea. Probiotics can also be administered throughout the duration of chemotherapy and have been anecdotally reported to decrease the frequency and severity of chemotherapy-induced diarrhea.

Cats that are unwilling to eat for several days or that have intractable vomiting should be hospitalized for supportive care with intravenous fluids to correct any hydration deficits and electrolyte abnormalities. Injectable antiemetics should be administered until the cat is eating readily on its own. Dosage of the particular chemotherapy agent should be reduced by 20% for cats that require hospitalization for significant gastrointestinal toxicosis.

Hematologic

Myelosuppression, particularly neutropenia, is a common sequela of chemotherapy administration. Most affected cats remain asymptomatic, but a small number may develop serious, life-threatening complications as a result of neutropenia and subsequent development of sepsis. The neutrophil nadir occurs approximately 7 to 10 days after chemotherapy administration, with exceptions to this noted in subsequent sections. To monitor for myelosuppression, a CBC should be checked before each chemotherapy administration to ensure that neutrophil and platelet counts are adequate. Treatment with chemotherapy should be delayed if the neutrophil count is less than 2000 to 3000 cells/uL or if the platelet count is less than 75,000 to 100,000 cells/uL. These ranges are merely guidelines, and CBC values should be assessed in conjunction with the overall health of the cat in mind. If neutropenia or thrombocytopenia occurs, a treatment delay of 5 to 7 days is generally recommended, at which time a CBC should be rechecked to ensure that cell counts have normalized. For chemotherapy agents that are administered every 2 to 3 weeks, a CBC should be checked 7 to 10 days after the first treatment with that drug. If neutrophil counts are greater than 1000 to 1500 cells/uL and the cat is afebrile and clinically well, reduction in subsequent doses is not needed.

Cats with neutrophil counts greater than 1000 cells/uL have a low risk of systemic infection. Most cats with significant neutropenia (≤1000 neutrophils/uL) can be managed on an outpatient basis, provided they are feeling well and afebrile. A broad-spectrum oral antimicrobial that is sparing to the normal gastrointestinal flora, such as trimethoprim–sulfa or enrofloxacin, can be administered for 5 to 7 days prophylactically. Cats that are febrile or systemically unwell with a concurrent neutropenia should be hospitalized for supportive therapy with intravenous fluids and antimicrobials to correct any hydration deficits or electrolyte abnormalities. In addition to a CBC, a biochemical profile and urinalysis should be obtained at admission. Treatment with intravenous broad-spectrum antimicrobials should be instituted until the cat is eating well and able to receive oral medications. Cats generally recover from febrile neutropenic episodes in 1 or 2 days. Cats that are slow to recover or are declining in the face of appropriate therapy should have thoracic radiographs, urine culture, and blood cultures performed to determine whether a resistant source of infection exists. Neutrophil counts need not be normal before the cat is released from the hospital as long as it is afebrile, eating, and tolerating oral medications.

Alopecia

Alopecia is a common concern for pet owners whose cat may require chemotherapy as part of its cancer treatment. Cats rarely develop diffuse alopecia, but this can happen with chronic administration of high-dose chemotherapy. Owners should be cautioned that most cats undergoing treatment with chemotherapy may lose their whiskers and other guard hairs, and previously shaved areas may be slow to regrow. Generally, hair will grow back once chemotherapy is discontinued.

Extravasation

Many intravenously administered chemotherapy agents are vesicants and can cause local tissue irritation or necrosis if administered outside of the vein. Of the more common chemotherapy drugs used in cats, doxorubicin, vincristine, and vinblastine are all vesicants. If there is any doubt as to whether a drug is a vesicant, it should be administered as though it is.

Signs of extravasation may include pain, erythema, moist dermatitis, and necrosis and may appear 1 to 10 days after extravasation of the drug.[28] If extravasation is suspected at the time of administration, the infusion should be stopped immediately. An attempt should be made to aspirate the drug with up to 5 mL of blood back into the syringe. The catheter is removed once this has been accomplished. Recommendations regarding additional treatment are generally extrapolated from experiences in human oncology and are based on the type of drug that was extravasated. In the case of vinca alkaloid extravasation, warm, dry compresses can be applied for several hours and hyaluronidase injected into the local site.[10] The volume of hyaluronidase injected should equal the volume of drug extravasated. Administration of dexrazoxane (Zinecard), a free-radical scavenger marketed to prevent doxorubicin-associated cardiotoxicity in humans, is indicated in the case of doxorubicin extravasation. The recommended dose is 1:10 of vesicant to dexrazoxane, and this should be administered intravenously through a separate catheter within 6 hours of extravasation.[10,30] Dexrazoxane is expensive and may be too costly for practitioners to stock. Availability at a local human hospital should be investigated because timely administration (within 3 to 6 hours) after extravasation may help mitigate tissue necrosis. Alternatively, topically applied dimethyl sulfoxide (DMSO) to the site of extravasation may help minimize tissue damage as

well.[51] Aggressive surgical débridement may be required to manage severe cases of perivascular necrosis.

Hypersensitivity Reactions

L-asparaginase and doxorubicin are drugs that may cause hypersensitivity reactions in cats. Cats receiving doxorubicin should be monitored for pruritus, head shaking, erythema of the skin and mucous membranes, facial edema, wheezing, and dyspnea during the doxorubicin infusion. If any of these signs are noted, the infusion should be stopped and the cat administered diphenhydramine (2 to 4 mg/kg intramuscularly) and dexamethasone SP (0.2 to 0.4 mg/kg intravenously). Once the reaction has subsided, then infusion can be restarted at a slower rate of administration. Treatment with L-asparaginase may result in anaphylaxis. This generally occurs within 60 minutes of administration and is more likely to occur with subsequent doses than the first dose. Cats that have been treated with L-asparaginase should be closely monitored for 60 minutes after treatment for respiratory difficulty, vomiting, diarrhea, and collapse. Aggressive supportive care may be required if anaphylaxis occurs. Cats that have previously experienced hypersensitivity reactions should be premedicated with diphenhydramine and dexamethasone SP before every subsequent dose of the drug to which they had the reaction. Reactions that are severe warrant discontinuation of the drug. Subsequent hypersensitivity reactions can be more severe or even life-threatening.

COMMONLY USED CHEMOTHERAPY DRUGS

This section deals with chemotherapy agents commonly used for treating cats with cancer, as well as some newer agents about which limited information is known. Table 28-1 summarizes these chemotherapy drugs, common indications, dosages, and associated toxicities.

Alkylating Agents

Chlorambucil (Leukeran)

Chlorambucil is an orally administered DNA alkylating agent that is used to treat low-grade lymphoma, chronic lymphocytic leukemia, and, less commonly, multiple myeloma. Reported dosages include 2 mg orally every 2 or 3 days, 2 to 4 mg/m^2 orally every other day, 15 mg/m^2 orally every day for 4 consecutive days once every 3 weeks, and 20 mg/m^2 orally once every 2 weeks.[13,23,49]

Chlorambucil is generally well tolerated, and gastrointestinal signs are uncommon. Myelosuppression may occur after prolonged used. Rare toxicities may include neurotoxicity, which has been reported in a single cat, and there may be an increased risk of developing a second malignancy with prolonged therapy.[4,49]

Cyclophosphamide (Cytoxan)

Cyclophosphamide is a prodrug that requires hepatic activation and is excreted primarily by the kidneys. It is most commonly combined with other chemotherapy drugs to treat lymphoma or various sarcomas. It can be administered either orally or intravenously, and dosages range from 200 to 300 mg/m^2 or 10 mg/kg, as dictated by the protocol used. Cyclophosphamide may be administered as a single bolus, or the oral dose may be divided over 3 to 4 days. For example, if the cat's total dose is 75 mg, then the cat may be administered a 25-mg tablet orally once daily for 3 days. Tablets should never be divided, and it may be necessary to compound cyclophosphamide for smaller cats. Alternatively, the injectable form is relatively inexpensive, and dosing is very flexible.

Common side effects include myelosuppression and gastrointestinal toxicity. Less commonly, sterile hemorrhagic cystitis may develop secondary to cyclophosphamide administration.[8] If signs of hematuria, pollakiuria, or stranguria are observed in a cat that has been recently treated with cyclophosphamide, a urinalysis and urine culture should be performed. If the urine culture is negative, a presumptive diagnosis of sterile hemorrhagic cystitis can be made, and cyclophosphamide therapy should be discontinued permanently.

Lomustine (CCNU, CeeNU)

Lomustine is an oral DNA alkylating agent that is most frequently used against mast cell tumors and lymphoma.[11,41,42] Because of its ability to cross the blood–brain barrier, it is also used to treat brain tumors, but efficacy against these tumor types is not documented in cats. It may be efficacious against fibrosarcoma and multiple myeloma.[11] Lomustine is administered at 50 to 60 mg/m^2 or 10 mg/cat orally once every 3 to 6 weeks.[11,41,42] It may be necessary to compound capsules to smaller sizes for more accurate dosing because the 10 mg/cat dose may underdose or overdose some cats.

Myelosuppression, particularly neutropenia, is the dose-limiting toxicity for lomustine. Severe and persistent thrombocytopenia can occur that warrants discontinuation of the drug if platelet numbers do not return to normal levels in 6 weeks. Gastrointestinal signs can occur with this drug as well. Hepatotoxicity has not been reported in cats to date, but routine monitoring of liver enzymes is still recommended. Pulmonary fibrosis can occur in people treated with CCNU, and a report of pulmonary fibrosis developing after chronic CCNU therapy exists for a single cat.[46] Renal toxicity is an uncommon side effect in humans and has not been reported in cats, but routine monitoring of kidney values

TABLE 28-1 **Commonly Used Chemotherapy Drugs**

Drug	Main Indications	Toxicities	Dosage
ALKYLATING AGENTS			
Cyclophosphamide	LSA, leukemia, sarcoma	Myelosuppression, GI, sterile hemorrhagic cystitis	200 to 300 mg/m^2 PO or IV or 10 mg/kg IV, depending on protocol used
Chlorambucil	Low-grade LSA, CLL, MM	GI and myelosuppression (uncommon)	2 mg PO every 2-3 days; 2-3 mg/m^2 PO every other day; 15 mg/m^2 PO × 4 days every 3 weeks; 20 mg/m^2 PO every 2 weeks
Lomustine	MCT, LSA	Myelosuppression, GI, pulmonary fibrosis (rare)	50 to 60 mg /m^2 PO or 10 mg/cat every 3 to 6 weeks
Melphalan	MM, LSA	Myelosuppression (thrombocytopenia)	0.1 mg/kg/day PO; 0.1 mg/kg PO every 24 hours for 14 days, then 0.1 mg/kg PO every other day
ANTHRACYCLINES			
Doxorubicin	LSA, various sarcomas and carcinomas	Myelosuppression, GI, nephrotoxicity, perivascular vesicant, hypersensitivity reaction	1 mg/kg or 25 mg/m^2 IV every 2-3 weeks
Liposome-encapsulated doxorubicin (Doxil)	ISS	GI, nephrotoxicity, perivascular vesicant, cutaneous, hypersensitivity	1 mg/kg IV every 3 weeks
Mitoxantrone	LSA, various sarcomas and carcinomas	GI, myelosuppression	6 to 6.5 mg/m^2 IV every 3 weeks
ANTIMETABOLITES			
Cytosine arabinoside	LSA, leukemia	Mild myelosuppression, GI	600 mg/m^2 SC, divided into 4 doses given every 12 hours for 2 days
Gemcitabine	SCC, other carcinomas	May cause increase hematologic and local tissue toxicity when used as a radiosensitizer	Not assessed as single agent in cats
Methotrexate	LSA	GI, myelosuppression	0.8 mg/kg PO or IV as directed by protocol
ANTITUBULIN AGENTS			
Vinblastine	MCT, LSA	GI, myelosuppression	Unknown, 2 mg/m^2 IV weekly or every other week
Vincristine	LSA, leukemia	GI, myelosuppression, peripheral neuropathy	0.5 to 0.75 mg/m^2 IV weekly
Vinorelbine	Not assessed	Not assessed	Not assessed
TYROSINE KINASE INHIBITORS			
Imatinib (Gleevec)	MCT, ISS	Mild GI	10 mg/kg PO daily
Masitinib (Kinavet)	Not assessed	Not assessed	Not assessed
Toceranib (Palladia)	Not assessed	GI	2.8 mg/kg PO every other day or Monday, Wednesday, Friday
MISCELLANEOUS			
L-asparaginase	LSA	Hypersensitivity	400 IU/kg or 10,000 IU/m^2 SC or IM
Carboplatin	Carcinoma or sarcoma	Myelosuppression; GI	240 mg/m^2 IV every 3-4 weeks
Imiquimod 5% cream (Aldara)	Cutaneous SCC *in situ* or actinic SCC	Localized erythema	Topical
Prednisone/ prednisolone	LSA, MM, MCT	GI, polyuria, polydipsia, polyphagia, diabetes mellitus	2 mg/kg PO once daily; taper according to protocol
Hydroxyurea	Polycythemia vera, chronic myelogenous leukemia	GI, myelosuppression	10 mg/kg PO daily

LSA, Lymphosarcoma; *GI,* gastrointestinal; *PO,* orally; *IV,* intravenously; *CLL,* chronic lymphocytic leukemia; *MM,* multiple myeloma; *MCT,* mast cell tumor; *ISS,* injection-site sarcoma; *SCC,* squamous cell carcinoma; *SC,* subcutaneously; *IM,* intramuscularly.

should be performed for cats with documented renal insufficiency that are receiving CCNU.

Melphalan

Melphalan is an oral DNA alkylating agent that is most commonly used in treatment of multiple myeloma and occasionally lymphoma. Melphalan can be administered at 0.1 mg/kg orally once daily or 0.1 mg/kg orally daily for 14 days followed by 0.1 mg/kg orally every other day.[5,7] Tablets may need to be compounded for more accurate dosing because they should not be split.

Myelosuppression, in particular thrombocytopenia, is the most common toxicity and generally occurs with chronic administration. A CBC should be monitored once weekly for the first month and then every 4 to 8 weeks during melphalan therapy.

Anthracyclines

Doxorubicin (Adriamycin)

Doxorubicin is an anthracycline that exerts its antineoplastic effects by way of a number of mechanisms, including topoisomerase II inhibition, intercalation of DNA, and generation of free radicals. Doxorubicin is commonly used in multidrug protocols for lymphoma, injection-site and other soft tissue sarcomas, and feline mammary carcinomas. Doxorubicin is diluted in 30 to 50 mL 0.9% NaCl and administered at 1 mg/kg or 25 mg/m^2 intravenously over 20 to 60 minutes every 2 to 3 weeks.

More common side effects of doxorubicin administration include gastrointestinal signs and myelosuppression. Doxorubicin is a potent vesicant, and utmost caution should be used to ensure that extravasation does not occur during administration. Cumulative nephrotoxicity may occur with doxorubicin administration, and this drug should not be used in cats with renal insufficiency.[36] Renal values and urine specific gravity should be monitored routinely in cats receiving doxorubicin and the drug discontinued if isosthenuria or azotemia occur. Cats can also have an acute hypersensitivity reaction with doxorubicin, and some practitioners routinely premedicate cats receiving doxorubicin with diphenhydramine or dexamethasone SP (or both). Regardless of whether premedication with antihistamines or corticosteroids is performed, the cat should be closely monitored during the infusion for any indications of a hypersensitivity reaction, such as head shaking, erythema of the pinna or mucous membranes, facial swelling, dyspnea, and agitation. Cumulative cardiotoxicity with doxorubicin administration is well documented in humans and dogs but is infrequent in cats.[36] Administration of doxorubicin to cats with underlying cardiac disease is discouraged, and some practitioners recommend not exceeding cumulative doses of 180 to 240 mg/m^2 in cats with normal cardiac function.

Liposmal-Encapsulated Doxorubicin (Doxil)

Liposomal-encapsulated doxorubicin was formulated to avoid the significant cardiotoxicity in humans that limits doxorubicin administration. This drug may have efficacy against similar tumor types as doxorubicin, including injection-site sarcomas, and is dosed at 1 mg/kg intravenously every 3 weeks.[40]

Liposomal-encapsulated doxorubicin has a similar toxicity profile in cats as native doxorubicin. Gastrointestinal side effects are generally mild and self-limiting. Liposomal-encapsulated doxorubicin is associated with nephrotoxicity, and renal function should be closely monitored after administration of the drug.[40] It is a vesicant and should be administered only through a cleanly placed intravenous catheter. Cats may also develop a nonpainful alopecia and erythema with hyperpigmentation around their mouths and distal limbs.[40] Cats may experience a hypersensitivity reaction characterized by salivation and bradycardia during their first treatment with liposomal-encapsulated doxorubicin; this can be managed with administration of diphenhydramine and dexamethasone SP.[40] Intracavitary administration of liposomal-encapsulated doxorubicin has been reported in dogs but has not been evaluated in cats.

Mitoxantrone

Mitoxantrone is an anthracycline derivative that exerts its cytotoxic effects by inhibiting topoisomerase II. This drug likely has a similar antitumor profile to doxorubicin and may be efficacious against lymphoma and various carcinomas and sarcomas.[35] The mitoxantrone dosage is 6 to 6.5 mg/m^2 intravenously every 3 weeks. The drug is diluted in 20 to 50 mL 0.9% NaCl before intravenous administration over 10 to 15 minutes. Mitoxantrone can be administered in the pleural or peritoneal space to help alleviate malignant effusions.

The most common adverse effects observed with mitoxantrone are mild, self-limiting gastrointestinal signs and myelosuppression. Unlike doxorubicin, mitoxantrone does not induce hypersensitivity reactions and is not as potent a vesicant if extravasated. Owners should be cautioned that urine and sclera may be blue-tinged after administration.[7]

Antimetabolites

Cytosine Arabinoside (Cytarabine, Cytosar-U, ara-C)

Cytosine arabinoside is a deoxycytidine analog that interferes with DNA synthesis through DNA polymerase inhibition. Because this drug is cell cycle specific with an extremely short plasma half-life, it is most efficacious when administered by constant-rate infusion or with the dose divided into twice-daily subcutaneous injections over several days. Cytosine arabinoside is used in cats

primarily to treat lymphoma or leukemia, particularly when there is central nervous system (CNS) involvement, because of the ability of the drug to cross the blood–brain barrier. Cytosine arabinoside is often substituted for cyclophosphamide for treatment of renal lymphoma because CNS involvement occurs in approximately 40% of these cases.[33] The dosage of cytosine arabinoside is 600 mg/m^2 divided into four doses administered subcutaneously twice daily for 2 days or administered as a constant-rate infusion at 300 mg/m^2 per day for 2 days.[7]

Cytosine arabinoside is generally well tolerated, with myelosuppression being most common and gastrointestinal signs occurring rarely.

Gemcitabine

Gemcitabine is an analog of deoxycytidine that is activated intracellularly, resulting in DNA synthesis inhibition. There is limited information on the use of gemcitabine as a single agent in cats. It has been used as a radiation sensitizer in the treatment of oral squamous cell carcinoma (SCC) and also in combination with carboplatin as therapy for various carcinomas.[22,29,31] This drug is expensive compared with other chemotherapy drugs, and optimal dosing in cats is not known at this time.

Adverse effects when administered intravenously at 2 mg/kg weekly in conjunction with carboplatin included moderate gastrointestinal toxicity and myelosuppression.[31] When administered intravenously at 25 mg/m^2 twice weekly as a radiation sensitizer, significant hematologic and local tissue toxicity occurred.[29] Additional research investigating efficacy, dosage, and toxicity of gemcitabine as a single agent drug is necessary before it can be used routinely in cats with cancer.

Methotrexate

Methotrexate is an antifolate that inhibits dihydrofolate reductase, thereby blocking DNA synthesis. It has been used primarily in combination chemotherapy protocols for lymphoma at a dosage of 0.8 mg/kg weekly, either intravenously or orally.[32,33,45]

Adverse effects of methotrexate administration are most commonly gastrointestinal signs, with myelosuppression occurring less commonly.

5-Fluorouracil (5-FU)

5-Fluorouracil (5-FU) is available in injectable and topical formulations. Because this drug has been documented to cause fatal neurotoxicity in cats, it should not be administered, even topically, to this species.[17,18,52]

Antitubulin Agents

Vinblastine and vincristine are naturally occurring vinca alkaloids derived from the periwinkle plant, and vinorelbine is a second-generation synthetic vinca alkaloid. These drugs disrupt cell division by binding to the microtubular proteins in the mitotic spindle. Metabolism of this class of drugs occurs in the liver, and dosage adjustments should be made for liver dysfunction. The antitubulin agents share a similar toxicity profile, with exceptions for each drug noted in subsequent sections. They are generally well tolerated, but mild gastrointestinal toxicosis and myelosuppression may occur. The antitubulin agents are all vesicants and should be administered using a cleanly placed catheter.

Vinblastine

Vinblastine is used as a treatment for mast cell tumor or substituted for vincristine in lymphoma protocols when vincristine is not tolerated by the cat or the disease has become refractory to vincristine in a rescue setting. Anecdotally, cats can tolerate intravenous dosages of 2 mg/m^2 weekly to every other week, but published data are lacking.

Vincristine

Vincristine is used commonly to treat lymphoma and leukemia; reported dosages range from 0.5 to 0.75 mg/m^2 given as an intravenous bolus once weekly. Peripheral neuropathy, which may present as constipation in cats, is uncommon but may occur with prolonged administration.[7]

Vinorelbine (Navelbine)

There is no published information regarding vinorelbine and its possible antitumor spectrum, dosage, or toxicity profile in tumor-bearing cats.

Platinum Drugs

Carboplatin

Carboplatin is a platinum-derived alkylating agent that may have efficacy against various carcinomas and sarcomas.[7,24] The most common route of administration is intravenous, but carboplatin can also be administered intracavitarily, in the thorax or abdomen, and intralesionally. Carboplatin is administered intravenously at 240 mg/m^2 every 3 to 4 weeks. Dosing of carboplatin on the basis of glomerular filtration rate has been investigated and may allow for more appropriate dosing in cats, but this is clinically impractical for most practitioners.[2,3] Carboplatin can also be used intralesionally for facial SCC. General anesthesia is required for treatment, and carboplatin is administered at 1.5 mg/cm^3 in purified sesame oil emulsion injected every 0.5 cm in the tumor and adjacent tissues weekly for up to four treatments.[53] Carboplatin has been reported to be administered intracavitarily at 180 to 200 mg/m^2 to help alleviate malignant effusions; however, information regarding efficacy is limited.[47,48]

Myelosuppression is the dose-limiting toxicity of carboplatin. Neutrophil and platelet nadirs generally occur 2 to 3 weeks after administration.[24] Gastrointestinal signs occur less commonly with carboplatin. Because carboplatin is excreted by the kidneys, it is important to assess renal function (blood urea nitrogen, creatinine, and urine specific gravity) before each treatment. Carboplatin is not commonly directly nephrotoxic, but decreased excretion occurs with decreased renal function, thereby increasing the likelihood of toxicity.

Cisplatin

Administration of cisplatin to cats induces a fatal pulmonary edema. It should not be administered to cats at any dosage.[25]

Tyrosine Kinase Inhibitors

Tyrosine kinases are proteins expressed on cell surfaces that are integral to regulation of cell growth and differentiation. These kinases, such as KIT, epithelial growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR), bind their specific growth factor, leading to downstream intracellular signaling and regulation of cell growth, differentiation, and survival. Tyrosine kinases can become constitutively activated with some types of cancer, thereby leading to unregulated cell growth. Tyrosine kinase inhibitors are a newer class of antineoplastic agents that inhibit these kinases by binding to the ATP-binding pocket, resulting in downregulation of cellular growth. Tyrosine kinase inhibitors used in veterinary oncology include imatibinib (Gleevec; Novartis), toceranib (Palladia; Pfizer), and masitinib (Kinavet CA-1; AB Science). Both toceranib and masitinib have recently been approved by the Food and Drug Administration for the treatment of canine mast cell tumors. Gastrointestinal side effects are common in dogs, and it is recommended that patients have a "drug holiday" until gastrointestinal signs resolve. Use of these drugs for cats remains off-label, and there is limited information regarding dosage, tumor specificity, efficacy, and toxicity of tyrosine kinase inhibitors in this species.

Imatinib (Gleevec)

Imatinib has been used to treat feline cutaneous, splenic, and disseminated mast cell tumors at doses at 10 to 15 mg/kg orally once daily. The most common side effects noted are mild gastrointestinal upset.[20,21,27]

Toceranib (Palladia)

Information regarding use of toceranib in cats is limited. Preliminary results suggest that dosage of 2.8 mg/kg orally every other day or on a Monday/Wednesday/Friday schedule may have some efficacy against oral SCC and injection-site sarcomas.[19] Most common side effects are gastrointestinal, particularly anorexia with weight loss and vomiting.[19]

Masitinib (Kinavet CA-1)

Masitinib has been administered to healthy cats at a dosage of 50 mg/cat orally every 24 to 48 hours and was well tolerated over a 4-week period.[9] Gastrointestinal toxicosis was most common, with neutropenia and proteinuria occurring less frequently.[9] There is no information at this time regarding dosage, safety, and efficacy for masitinib in cats with cancer.

Miscellaneous

L-asparaginase

L-asparaginase is an enzyme derived from *Escherichia coli* that depletes cells of asparagine, an essential amino acid for protein synthesis. Lymphoreticular cells are particularly sensitive to the effects of L-asparaginase because they lack asparagine synthetase and cannot produce asparagine. For this reason L-asparaginase is primarily used in treatment of lymphoma and leukemia. It is administered at 400 mg/kg or 10,000 IU/m^2 intramuscularly or subcutaneously as part of a multidrug protocol.

The most common toxicity associated with L-asparaginase administration is anaphylaxis, which may be characterized by dyspnea, pruritus, edema, vomiting, diarrhea, hypotension, and collapse. Additional rare side effects may include myelosuppression, particularly when administered simultaneously with vincristine, or pancreatitis.

Hydroxyurea

Hydroxyurea is an oral chemotherapy agent that suppresses proliferation of myeloid, erythroid, and platelet precursors by inhibiting DNA synthesis.[37] The main indications for hydroxyurea are treatment of polycythemia vera and chronic myelogenous leukemia. The recommended dosage is 10 mg/kg orally once daily.[7]

Side effects associated with hydroxyurea therapy in cats may include myelosuppression and gastrointestinal toxicity.[7]

Imiquimod (Aldara)

Imiquimod 5% cream (Aldara) is a topical immune response modifier that has been shown to have antitumor effects by enhancement of both innate and cell-mediated immunity. Data are limited at this time, but imiquimod 5% cream may be effective in treating multifocal, cutaneous SCC *in situ* or actinic (solar-induced) SCC in cats.[14,38] Reported topical application schedules range from once daily to three times a week on affected areas.

Adverse events that have been reported include mild erythema at the site of application.[14,38] Potential systemic toxicities have been reported as well, and these are likely secondary to ingestion of imiquimod 5% cream by the cat because the drug should not have systemic effects when applied topically. These side effects include mild gastrointestinal upset, neutropenia, and elevated liver enzymes.[14] It is recommended that routine monitoring of CBC and biochemistry panel be performed every 4 to 8 weeks in cats treated with imiquimod 5% until more information is known about this drug in cats.

Prednisone and Prednisolone

Prednisolone and its prodrug prednisone are glucocorticoids frequently used in veterinary oncology. In most species prednisone is converted to prednisolone in the liver, but there is some concern that this step does not occur efficiently in some cats. Therefore use of prednisolone rather than prednisone is recommended in this species.[39] Prednisolone is commonly used in multidrug chemotherapy protocols, and there is evidence that prednisolone has activity against lymphoma, plasma cell tumors, and mast cell tumors.* The antitumor dose of prednisolone is 2 mg/kg orally once daily. This dose is tapered over approximately 1 month and then generally discontinued when used in combination chemotherapy protocols. Other common uses for prednisolone include decreasing edema associated with tumors of the CNS and as an antiinflammatory for pain control in cats that cannot tolerate administration of nonsteroidal antiinflammatory drugs. For these indications, prednisolone is generally administered at antiinflammatory dosages (0.5 to 1 mg/kg orally once daily).

Prednisolone is generally well tolerated in cats. Adverse effects may include polyphagia, polydipsia, polyuria, and gastrointestinal irritation. Rarely, chronic high-dose prednisolone therapy may lead to development of diabetes mellitus in cats.[12]

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SELECTED FELINE CANCERS

Cats are affected by a wide variety of cancers and a complete discussion is beyond the scope of this chapter. In general, information on the most common cancers will be found elsewhere in this book with the relevant body system. Presented here is an overview of three important cancers that deserve more in-depth discussion—lymphoma, injection-site sarcoma, and mammary tumors. For more detailed information on feline oncology, the reader is referred to a current textbook, such as *Cancer Management in Small Animal Practice*, edited by Carolyn Henry and Mary Lynn Higginbotham (St. Louis, 2010, Saunders).

LYMPHOMA

Kevin Choy and Jeffrey N. Bryan

INCIDENCE, ETIOLOGY, AND RISK FACTORS

Lymphoma (also termed *malignant lymphoma* and *lymphosarcoma)* is the most common feline neoplasm, comprising more than half of all hemolymphatic tumors.[29,39,54] Lymphoma can be found in cats of any age, breed, or sex, although purebred cats such as the Manx, Burmese, and Siamese may have an increased risk.[16,25,29,39,54] The precise etiology of feline lymphoma in many cases is unknown; however, viral causes of feline lymphoma are well defined, with both feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infections implicated. Before the widespread use of FeLV testing and control regimens that began in the 1980s, up to 70% of diagnosed feline lymphoma was caused by FeLV infection. Over the following decades a shift away from FeLV-associated tumors has been seen, with only 14% to 25% of cats with lymphoma having documented FeLV infection despite an overall increase in diagnosed cases

of feline lymphoma.* Although FeLV has a direct role in tumorigenesis, FIV is thought to indirectly contribute to an increased risk of feline lymphoma by immunosuppression.[2,17] This association with immune compromise is further supported by a report describing 95 feline renal transplant patients receiving immunosuppressive therapy, in which 9.5% of cats developed *de novo* malignant neoplasia, predominantly lymphoma.[55] FeLV infection in one study increased the risk of lymphoma 62-fold, FIV infection sixfold, and concurrent FeLV and FIV infection 77-fold.[44] Exposure to second-hand cigarette tobacco smoke is also reported to increase the risk of developing lymphoma 2.4- to 3.2-fold over background, depending on duration of exposure.[3] Chronic inflammation may also play a role in the development of feline lymphoma, as seen in other tumors, such as injection-site sarcomas.[26] An association has been suggested between inflammatory bowel disease and intestinal lymphoma in which one progresses to the other, although supporting evidence is not well developed.[6,26,34,41,42]

CLINICAL FEATURES

Cats with lymphoma exhibit a bimodal pattern of clinical presentation. The first group comprises cats approximately 2 years of age (although cats as young as 6 months have been reported) with FeLV-associated disease, typically with mediastinal lymph node involvement and pleural effusion resulting in dyspnea.[16] The second group comprises mature cats 6 to 12 years of age that are serologically FeLV negative and present with alimentary (particularly intestinal) lymphoma or lymphoma in a multicentric or extranodal pattern.[8,25] Clinical signs of alimentary lymphoma commonly include vomiting, diarrhea, anorexia, and weight loss. A palpable abdominal mass or thickening of the intestinal tract is often appreciated. Nonalimentary locations for lymphoma are quite varied and can include virtually every tissue in the body; renal, mediastinal, respiratory (particularly nasal), CNS (brain and spinal), multicentric (lymph node), skeletal muscle, cutaneous, conjunctival, and cardiac lymphoma have been reported, with clinical signs referable to the respective organ system dysfunction.† Hypercalcemia may also be a feature of lymphoma, but this is seen less commonly than in canine lymphoma.[4] Prevalence, presenting clinical signs, and biological behavior of feline lymphoma vary significantly with geographical location and may reflect regional differences in feline populations as well as differences in retroviral strains and prevalence.‡

DIAGNOSIS AND STAGING

Because feline lymphoma is a neoplasm of the lymphoid system that generally affects multiple locations, a thorough diagnostic evaluation is recommended to confirm diagnosis and anatomic localization(s) and establish baseline data points to evaluate response to subsequent therapy. Feline lymphoma is usually classified on the basis of anatomic location rather than the traditional World Health Organization (WHO) staging scheme commonly used in dogs. Anatomic site of origin is important insofar as each type of lymphoma appears to have different specific clinical behavior, therapy considerations, and prognosis.[5,8,29,34,54]

Diagnosis of most anatomic forms of lymphoma in the cat can be made from cytologic examination of fine-needle aspirates of an enlarged lymph node, affected tissues, or cavitary fluids (e.g., pleural effusions in mediastinal lymphoma). When cytologic findings are equivocal, histopathology and immunohistochemistry are recommended. Histopathology is particularly important in alimentary lymphoma in which endoscopic (partial thickness) or surgical (full thickness) biopsies of the gastrointestinal tract are generally required for a diagnosis to differentiate between severe lymphoplasmacytic intestinal inflammation and malignant lymphoma. Inclusion of the intestinal muscularis is necessary for a definitive diagnosis of lymphoma. If histopathology is inconclusive, molecular analysis techniques such as polymerase chain reaction for antigen receptor rearrangement (PARR) test for T and B cell receptor gene clonality assessment can provide further support for malignancy, but this is not yet established as a gold standard for diagnosis. Nasal lymphoma also commonly requires a biopsy using a blind or rhinoscopic approach to confirm diagnosis, with advanced imaging such as CT helpful in assessing the extent of disease.[49]

After the diagnosis of lymphoma, complete staging should include a detailed physical examination, with particular attention to lymph node size (including tonsils), abdominal palpation (masses, thickened intestinal loops, organomegaly), cranial thoracic compression (mediastinal mass), and ophthalmic examination. Peripheral lymphadenopathy is less common in cats than in dogs. Laboratory evaluation should include a CBC, serum biochemistry profile, urinalysis with culture and sensitivity (to assess for preexisting urinary tract infections that may represent a nidus for sepsis during immunosuppressive chemotherapy), and FIV and FeLV serology. Three-view thoracic radiographs (right lateral, left lateral, and ventrodorsal views) should be made to assess lymph node, pulmonary, mediastinal, and pleural structures. Abdominal ultrasound examination is useful to assess gastrointestinal wall thickness, mesenteric lymph node size, and organ size and echotexture (liver,

*References 1, 5, 7, 13-16, 25, 27, 29, 48, 50, 54.

†References 1-3, 5-8, 16, 17, 25, 26, 29, 30, 34, 41, 42, 44, 52.

‡References 7, 13-16, 27, 48, 50.

spleen, kidney). Ultrasound-guided fine-needle aspirates should be performed where appropriate. Bone marrow aspirates should be performed to evaluate this compartment for disease infiltration. Complete staging with anatomic classification will guide appropriate therapy selection, minimize toxicity, and reduce therapy-associated complications.

BIOLOGICAL BEHAVIOR

As with dogs, most anatomical classifications of feline lymphoma are non-Hodgkin–like disease that tends to progress to systemic involvement during the course of disease.[19,51] Because of the anatomic syndromic nature of lymphoma in cats, the clinical signs associated with the site of origin are most important for prognostication. Immunophenotype for B- or T-lymphocytes varies by location and etiology but has not been shown to be significantly prognostic for outcome.[1,5,30,37,54] Age, weight, sex, FIV status, and stage (based on WHO criteria) also do not appear to be prognostic in cats.[30,32] FeLV infection has been shown by some studies to be a negative prognostic factor because of a more rapid emergence of drug resistance, but other studies have not found a similar association.[1,11,50] The most important prognostic factor for feline lymphoma is response to therapy and anatomic localization of disease.

TREATMENT AND PROGNOSIS

Systemic chemotherapy is the primary treatment modality for feline lymphoma. Without medical therapy mortality rates in cats with lymphoma are approximately 40% and 75% at 4 and 8 weeks after diagnosis, respectively.[20] For aggressive high-grade lymphoblastic lymphoma, multi-agent chemotherapy is considered the standard of care, with a variety of protocols and response rates reported. There is a general lack of consensus regarding the gold-standard protocol. Consequently, many treatment regimens are specific to a particular institution or practice.

The combination protocol COP (cyclophosphamide, vincristine, and prednisone) has been reported to result in complete remission in 50% to 75% of cats, with a median survival time (MST) ranging from 2 to 9 months.[32,47,48] Single-agent doxorubicin chemotherapy has been less successful, with a response rate of 42% and median duration of response of 64 days in cats.[23,38] However, when doxorubicin is included into multi-agent protocols either as part of a CHOP (H = doxorubicin) protocol or as maintenance therapy (COP followed by doxorubicin), significantly longer durations of remission have been reported in cats that responded compared with cats that received only COP therapy.[32,47] These reports suggest that a subset of cats may benefit from the addition of doxorubicin. Doxorubicin should be used with caution in cats because it is potentially nephrotoxic and cardiotoxic; thus a COP-based protocol may be preferable for cats with preexisting renal or cardiac disease.[35] The doxorubicin-containing CHOP protocol that is used at Washington State University is provided (Table 28-2), but consultation with a veterinary oncologist is recommended before starting induction therapy. The most reliable prognostic indicator is response to therapy; individuals achieving complete remission typically enjoy the best outcomes, with MST approaching 1 year, and longer-term survival reported. Conversely, failure to achieve complete remission is generally associated with MST of a few months.[6,11,30,42,47] Single-agent therapy with prednisolone at 2 mg/kg

TABLE 28-2 Modified Madison-Wisconsin (Short) Protocol for Feline Lymphoma at Washington State University

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Vincristine	•		•			•		•			•				•				•			•		
Cyclophosphamide		•					•						•								•				
Doxorubicin				•					•								•								•
Prednisone	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Complete blood counts are performed before and weekly after each dose of chemotherapy. If the total segmented neutrophil count is below 2500, treatment is delayed for 1 week or until count increases above 2500. Watch for sterile hemorrhagic cystitis resulting from cyclophosphamide therapy. Serum biochemistry profiles and urinalysis should be checked once monthly to monitor for potential nephrotoxicity associated with doxorubicin therapy.
Vincristine: 0.5 mg/m^2 intravenously (do not exceed 0.12 mg/dose); *vesicant*.
Cyclophosphamide: 200 mg/m^2 intravenously or orally; *wear gloves if given orally*.
Doxorubicin: 25 mg/m^2 intravenously. Dilute into 50 mL of saline and administer intravenously over 40 to 60 minutes; *severe vesicant*.
Prednisone: 2 mg/kg orally daily for the first 2 weeks, then 1 mg/kg orally daily for the next 2 weeks, then 1 mg/kg orally every other day thereafter for long-term use.

orally once daily for 2 weeks and then tapered to 1 mg/kg thereafter may provide varying degrees of palliation, with reported MST of approximately 60 days.[1,47] Rescue protocols are not well defined in cats. Single-agent lomustine (CCNU) has been used in cats as primary therapy or in a rescue setting at reported dosages of 50 to 65 mg/m^2 orally every 3 to 6 weeks depending on degree and duration of myelosuppression. The advantages are simplicity and relative inexpensiveness, but response rates are variable, with generally shorter MSTs reported. Chronic administration of lomustine has been associated with severe thrombocytopenia and pulmonary fibrosis in cats.[1,5,21,40,45] Cats with renal lymphoma have been shown to have a reduced risk of CNS metastasis with the addition of cytosine arabinoside to a standard COP protocol (COAP).[5,31]

Malignant lymphocytes are radiosensitive, and radiation therapy has been reported for treatment of localized lymphoma.* Although radiation is effective for control of local disease, particularly nasal lymphoma, adjunctive systemic chemotherapy is generally advised to target residual tumor cells and delay systemic progression. Survival times of cats treated by localized radiation therapy with or without chemotherapy for nasal lymphoma often exceed 1 year, with durable MSTs approaching 3 years reported.[9,10,12,18,43] Whole-abdomen irradiation has also been used as adjunctive or rescue therapy for gastrointestinal lymphoma. In one pilot study eight cats with gastrointestinal or abdominal lymphoma that achieved remission during an abbreviated 6-week CHOP chemotherapy protocol received abdominal radiation therapy 2 weeks later. Five cats remained in remission for at least 266 days after starting therapy, with a range from 266 to 1332 days.[53] In another study a rapid abdominal radiation protocol delivered over 2 days for cats with relapsed or chemotherapy-resistant gastrointestinal lymphoma resulted in a response in 10 of 11 cats, with a postirradiation MST of 214 days.[36]

Large granular lymphoma is an uncommon, morphologically distinct variant of lymphoma in cats that carries a poor prognosis. Response to chemotherapy is generally poor, and an MST of 57 days after diagnosis has been reported.[22]

Feline alimentary lymphoma presents a therapeutic challenge. MSTs for cats experiencing complete remission can exceed 11 months.[24,42,45,56] High-grade lymphoblastic forms of alimentary lymphoma should be treated with combination chemotherapy (COP, CHOP). Low-grade small-cell gastrointestinal lymphoma (also termed *lymphocytic intestinal lymphoma)* is considered an indolent neoplasm that can be successfully treated with a combination of daily prednisone or prednisolone (2 to 3 mg/kg orally daily tapering to 1 mg/kg orally every 48 hours) and chlorambucil therapy (20 mg/m^2 orally every 2 weeks or 15 mg/m^2 orally every 24 hours for 4 consecutive days every 3 weeks). Prognosis was reported to be good, with overall response rates of up to 96%, up to 76% of cats achieving complete remission, and median clinical remission durations of approximately 19 to 26 months reported.[24,42,46,56] Please refer to Chapter 23 for further information on the management of gastrointestinal lymphoma.

Regardless of the anatomic form, most cats with lymphoma benefit from supportive care, particularly cats that are anorexic, vomiting, or severely debilitated because of chronic disease progression. Nutritional and fluid support is critical for cats that are inappetent because of either the malignancy or the chemotherapy. The placement of an esophageal, gastric, or jejunal feeding tube (bypassing the affected tissues) is often quite helpful to allow adequate nutrition, hydration, and administration of oral medication, particularly during early stages of treatment. Appetite stimulants, antiemetics, and thorough nursing care may also be necessary to improve body condition and tolerance to therapy.[34,54]

*References 9, 10, 12, 18, 19, 28, 36, 43, 53.

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INJECTION-SITE SARCOMA

William C. Kisseberth

INCIDENCE, ETIOLOGY, AND RISK FACTORS

Injection-site sarcomas, also referred to as vaccine-associated sarcomas, were first recognized as a distinct histopathologic and clinical entity 20 years ago, when an increase in the number of feline fibrosarcoma biopsy accessions was first observed.[13] The increased number of fibrosarcomas in cats could largely be explained by an increase in the number of tumors occurring at anatomic sites commonly used for vaccination (e.g., hindlimb, dorsal neck/interscapular, dorsal lumbar, flank, and dorsolateral thorax). It also was observed that the increase in tumor incidence coincided with significant changes in routine vaccination practices used in cats, notably the introduction of FeLV vaccines and legally mandated rabies vaccination of cats.[13] Often, sarcomas occurring at these locations were surrounded by lymphocytes and macrophages containing foreign material identical to that previously described in postvaccinal inflammatory injection site reactions.[13,14] Furthermore, the foreign material was found to contain aluminum, which is commonly used in vaccine adjuvants.[13] Although aluminum-adjuvanted rabies vaccines were the first to be associated with sarcoma formation in cats, subsequent epidemiologic studies identified an increased risk for sarcoma formation associated with other vaccines and other types of injections in cats, including adjuvanted and nonadjuvanted rabies, FeLV, and feline viral rhinotracheitis/calicivirus/panleukopenia vaccines, long-acting penicillins, and methylprednisolone acetate injections.[14,17,18] However, no specific manufacturer's product has ever been identified as being of greater risk.[18] Apparently, not all injectable products are associated with the same risk. For example, diabetic cats receiving frequent insulin injections (and probably other injections associated with hospitalizations) were not found to be at increased risk for sarcoma formation.[17]

The hypothesized pathogenesis of sarcoma formation in cats induced by injections is that inflammatory and immunologic reactions associated with the presence of foreign material in injection sites predisposes the cat to a derangement of its fibrous connective tissue repair response, eventually leading to neoplasia in some cases.[13] In fact, in some tumors transitional areas can be identified, where microscopic foci of sarcoma are found in areas of granulomatous inflammation. It has been pointed out that there is precedent for this type of oncogenesis in the cat.[13] Sarcomas have been reported to develop in the eyes of cats after persistent or previous trauma.[7] The pathogenesis of ocular sarcomas could be similar to that proposed for injection-site sarcomas. Although the histologic, epidemiologic, and clinical evidence supports an important role for injections in sarcoma formation in cats, other host and environmental factors also must be of critical importance because only a very small proportion of injections result in sarcoma formation. Although there is a feline sarcoma virus, it does not have a role in the pathogenesis of these tumors. Similarly, FeLV, FIV, papillomavirus, and polyomavirus viruses have all been undetectable in feline injection-site sarcomas and do not appear to have a role in pathogenesis.[8,19-21] The expression of a variety of oncogenes, tumor suppressor genes, and growth factors has been investigated in feline injection-site sarcomas, including p53, PDGF-R, KIT, TGF-alpha, FGFb, and STAT3.[15,25,27,30] A variable proportion of injection-site sarcomas exhibit dysregulated expression of each of these proteins; however, their role, if any, in pathogenesis is unclear at this time. In a recent study both injection-site sarcomas and spontaneous sarcomas in cats exhibited an extensive range of genomic imbalances, some of which were highly recurrent. Interestingly, deletions of two specific regions were significantly associated with the non–injection-site sarcoma (spontaneous) phenotype.[31]

The true incidence of injection-site sarcomas is unknown. The most common estimate given is between 1 of 1000 and 1 of 10,000 vaccines administered; however, a more recent epidemiologic study estimated the incidence of vaccine-associated sarcoma to be 0.63 sarcoma in 10,000 cats vaccinated and 0.32 sarcoma in 10,000 doses of all vaccines administered.[4,12,26] Thus the incidence is now believed to be one case for every 10,000 to 30,000 cats vaccinated.

CLINICAL FEATURES

The clinical presentation of injection-site sarcoma is that of a subcutaneous or intramuscular mass occurring at the site of a previous injection (although an injection history may not be known) (Figure 28-1). Injection-site sarcomas are most commonly located in the dorsal thoracic region between the shoulder blades, a common location for vaccination and other injections in cats. Other affected areas include the femoral, flank, lumbar, and gluteal regions; however, there is some evidence for a changing anatomic distribution of these tumors, presumably related to current vaccine administration recommendations made in response to this disease.[18,29] In the case of vaccine-associated sarcomas, tumors have been reported to form 4 weeks to 10 years after vaccination, although most appear to develop within 3 years.[12,24] Masses are typically nonpainful and firm to fluctuant and may contain cystic areas. Occasionally, large masses are ulcerated. Usually, affected cats show no systemic signs of illness, except in advanced disease. Feline

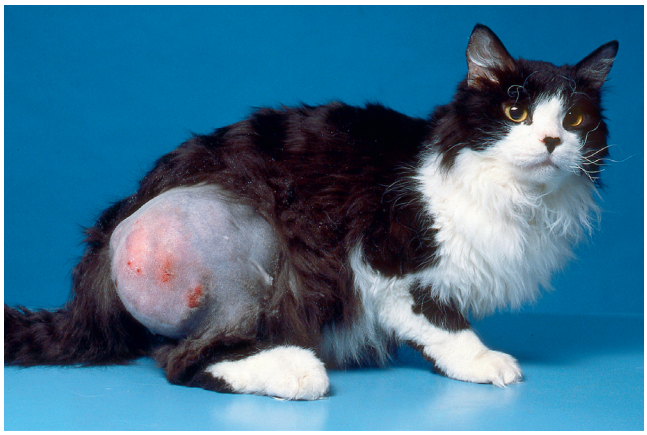

FIGURE 28-1 Injection-site sarcoma arising from the caudal thigh of a cat. *(Courtesy C. Guillermo Couto.)*

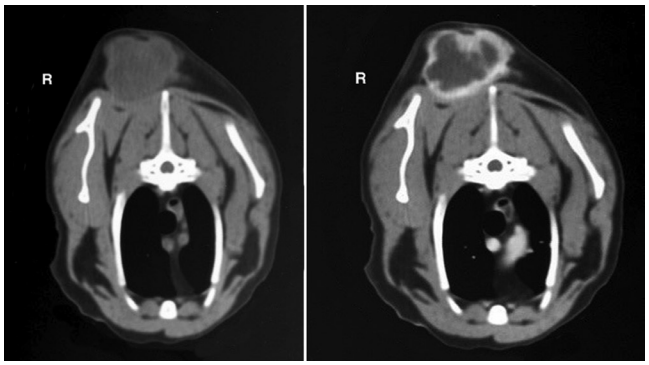

FIGURE 28-2 Computed tomography image of a contrast rim enhancing interscapular injection-site sarcoma in a cat. *(Courtesy Eric Green.)*

injection-site sarcomas are highly aggressive and locally invasive, making them challenging to treat. They are more likely to recur after surgical excision than spontaneous sarcomas at other sites.[14] Histologic subtypes of soft tissue sarcomas reported at the site of vaccination include fibrosarcoma, malignant fibrous histiocytoma, osteosarcoma, rhabdomyosarcoma, undifferentiated sarcoma, liposarcoma, and chondrosarcoma.[15]

Although injection-site sarcoma is the primary differential diagnosis in most cases, differential diagnoses may include other tumors (e.g., lymphoma), abscess, foreign body, and postvaccine reaction. Local vaccine or injection reactions in particular must be distinguished from sarcoma. In response to the recognition of injection-site sarcoma as a significant and iatrogenically caused health problem in cats, the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) was created.[32] VAFSTF concluded that owner education is imperative and cat owners should be warned of the risk of vaccine- and injection-associated sarcomas and the occurrence of local vaccine and injection reactions. Furthermore, owners should be taught how to examine the injection site and seek veterinary assistance if any of the three following scenarios occur (i.e., the "3-2-1" recommendation):

- A mass persists at the injection site for more than 3 months after injection.
- A mass is present and is larger than 2 cm, regardless of time since injection.
- A mass is still increasing in size 1 month after injection.[32,33]

DIAGNOSIS AND STAGING

A presumptive diagnosis of injection-site sarcoma can often be made on the basis of history, anatomic location, and fine-needle aspiration cytology; however, a biopsy should be performed to confirm the diagnosis. Tru-Cut needle biopsy, punch biopsy, or wedge biopsy is recommended, and the practitioner should strictly follow standard biopsy techniques and principles. Staging of injection-site sarcoma includes a minimum database consisting of a CBC and differential, serum chemistry profile, urinalysis, and FeLV and FIV serology. If regional lymph nodes are accessible for fine-needle aspiration cytology, they should be aspirated. Thoracic radiographs are made to assess for lung metastasis. CT or MRI imaging is extremely useful for assessing tumor invasiveness into surrounding structures and for surgical and radiation therapy planning (Figure 28-2).

BIOLOGICAL BEHAVIOR

Injection-site sarcomas are aggressive, locally invasive tumors with a moderate metastatic potential. Primary tumors grow at a variable rate, invading surrounding and underlying tissues and making surgical resection difficult. Metastasis occurs primarily in the lungs but also can occur at other sites, such as regional lymph nodes, mediastinum, pericardium, liver, pelvis, and eye.[9,10,28] Lung metastases are radiographically visible in 10% to 24% of the cases at the time of diagnosis.[5,16]

TREATMENT AND PREVENTION

Although injection-site sarcomas have the potential for metastasis, treatment is focused on local control of the primary tumor, at least initially. Because injection-site sarcomas are aggressive and locally invasive, establishing control of the primary tumor is often challenging. Treatment generally begins with wide and sometimes radical surgical excision of the primary tumor, provided the mass is determined to be surgically resectable using multiplanar imaging. Aggressive resection should include at least 3-cm lateral surgical margins and be one

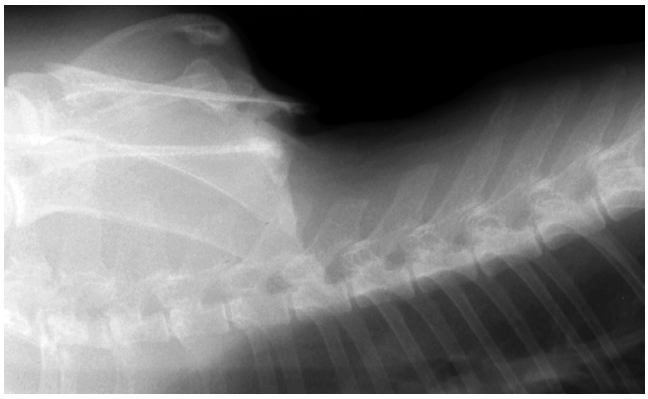

FIGURE 28-3 Postsurgical lateral radiograph of a cat with an interscapular injection-site sarcoma. Removal of vertebral dorsal processes was required to achieve complete resection. *(Courtesy Stephen J. Birchard.)*

uninvolved fascial layer deep. Because of the invasive nature of these tumors, depending on the anatomic location it may also be necessary to resect bony structures. Partial scapulectomy and removal of dorsal processes of vertebrae may be necessary with interscapular masses (Figure 28-3) and rib resections, and body wall reconstructions may be required to adequately resect masses affecting the body wall and flanks.[22] Masses occurring in the pelvic limb are often best managed by limb amputation or hemipelvectomy, provided the mass is distal enough to obtain a clean surgical margin. Surgical staples should be placed in the tumor bed to define the margins of the surgical field if radiation therapy will potentially be included in the postsurgical treatment plan. The margins of the excised mass should be clearly marked with surgical ink or suture before fixing and submitting for histopathology.[11] The best surgical outcomes are associated with aggressive surgeries performed by specialist surgeons.[16] The median recurrence-free interval for injection-site sarcomas excised at a referral institution was 274 days, significantly longer than a median of 66 days in those cats whose tumors were excised by referring veterinarians.[16] Even with aggressive wide excision, surgical margins are often infiltrated with neoplastic cells.[11] Overall, the local recurrence rate is 30% to 70%, and even when no evidence of tumor cells is detected histopathologically at the surgical margins, there may be a 50% local recurrence rate.[3,24] For this reason the decision to incorporate postoperative radiation therapy in the treatment plan of these patients should not unduly rely on whether tumor-free surgical margins are achieved. Cats treated with aggressive excision at first attempt have longer tumor-free intervals than those treated with marginal excision (325 days versus 79 days), and cats with complete excision have a longer tumor-free interval (>16 months versus 4 months) and survival time (>16 months versus 9 months) than those whose excisions were incomplete.[6,16]

Although surgical excision is the primary treatment modality for most cats with injection-site sarcomas, a multimodality treatment approach may provide better outcomes for cats with incomplete surgical excisions (whether or not the surgical margins are assessed to be "clean"). Radiation therapy can be incorporated into the treatment plan either preoperatively or postoperatively. There is no clear evidence as to whether preoperative or postoperative irradiation is better for injection-site sarcoma. In one study evaluating the effectiveness of preoperative radiation and surgery in 33 cats, the median disease-free interval was 398 days and the median overall survival time was 600 days.[5] Local recurrence of the tumor was noted in 45%. In another study 76 cats received postoperative radiation. The median disease-free interval was 405 days, and the median overall survival time was 469 days. The local recurrence rate was 41%.[3] Because these are different studies, with different confounding factors, results are not directly comparable. No clinical study has ever directly compared the two treatment approaches. When used, radiation treatment is typically performed in conjunction with surgery, except in the palliative setting.

The role of chemotherapy in the treatment of injection-site sarcoma is poorly defined. There are no studies that support its use as the primary, or sole, form of treatment in the gross disease setting and little evidence for its use in the adjuvant (after surgery or radiation) setting either. Nonetheless, chemotherapy is commonly used in an attempt to palliate nonresectable tumors; in the neoadjuvant setting to cytoreduce large tumors before surgery; and in the adjuvant setting, especially for histologically high-grade tumors. It has also been used as a radiation sensitizer. Chemotherapy drugs that have been used clinically include doxorubicin, cyclophosphamide, carboplatin, mitoxantrone, and vincristine.[24] In general, use of these drugs has resulted in some partial responses and infrequent complete responses. Usually, responses are not durable. Of these drugs doxorubicin has received the most attention, both as a single agent and in combination with cyclophosphamide. In one study evaluating the use of combined doxorubicin and cyclophosphamide in cats with nonresectable tumors, the overall response rate was 50%, with 17% having resolution of all clinically detectable tumor.[1] Unfortunately, the responses were not durable, with a median response duration of 125 days. In another study 69 cats were treated with four cycles of doxorubicin combined with surgical excision 10 days after the second chemotherapy cycle. No differences in the rates of recurrence or overall survival were found between the groups.[23] Several studies have investigated multimodality treatment, combining preoperative or postoperative radiation, surgery, and/or chemotherapy. One study compared surgery and radiation therapy with or without doxorubicin, and the other compared surgery and radiation therapy with or without doxorubicin and

cyclophosphamide.[2,3] No significant differences between the group receiving adjuvant chemotherapy and the group that did not were found in either study for overall survival or median time to recurrence.

In conclusion, aggressive wide surgical excision performed by an experienced specialist surgeon that includes advanced imaging in the treatment planning is recommended for most cats with injection-site sarcomas. There is evidence that some cats may benefit from preoperative or postoperative radiation therapy. The role for chemotherapy in a multimodality approach for this disease remains to be defined; however, its continued empiric use is reasonable in light of the lack of definitive studies addressing its efficacy and the potential benefits some drugs might provide.

Based on what is known and suspected regarding the pathogenesis of injection-site sarcomas in cats, prevention strategies are likely to have the greatest impact in decreasing the morbidity and mortality rates associated with injection-site sarcoma in the pet cat population. The VAFSTF and others have suggested strategies and guidelines that may help decrease the incidence of injection-site sarcoma and decrease morbidity and mortality rates. In addition to the 3-2-1 recommendations for management of vaccine reactions, it is recommended that rabies vaccines be administered as far distally as possible in the right rear limb; FeLV vaccines (unless containing rabies antigen as well) be given as distally as possible in the left rear limb; and vaccines containing any other antigens except rabies or FeLV be given on the right shoulder, with care taken to avoid the midline or interscapular space.[32] The location of the injection should be in an area that is amenable for possible surgical removal. The vaccination site, dose, manufacturer, and lot number should be accurately recorded.[33] The recommended vaccination protocols for cats are critically important, with the understanding that these protocols should be tailored to the individual needs of the patient.[26] Additionally, discussion with cat owners regarding vaccination practices and sarcoma risk should be part of routine client education by veterinarians.

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MAMMARY TUMORS

Kevin Choy

INCIDENCE, ETIOLOGY, AND PATHOGENESIS

Mammary tumors are the third most common feline tumor, accounting for up to 17% of all neoplasms in female cats.[6,10,19,24] Male cats can also be affected by mammary tumors, although much less often, with reported incidence of up to 5% compared with females.[9,31] Domestic short hair and Siamese breeds appear to have an elevated risk for mammary tumors.[9,24] Mammary neoplasia is generally seen in older cats with a median age of 10.8 years (mean 10 to 12 years), although cats as young as 9 months have been reported to be affected.* The precise etiology of feline mammary tumors is uncertain, but hormones, particularly estrogen and progesterone, are thought to play a significant role in tumorigenesis.[22] In a case control study, cats that underwent ovariohysterectomy before 6 months and 1 year of age had a 91% and 86% reduction in risk, respectively, of developing mammary carcinoma compared with intact cats.[22] Parity was not found to significantly affect risk for tumor development.[22] Both female and male cats regularly exposed to exogenous progestins or estrogen–progestin combinations such as medroxyprogesterone acetate have been identified to be at increased risk of developing mammary carcinoma.[15,17,22,28]

*References 9, 10, 18, 23, 24, 27, 31.

FIGURE 28-4 Gross appearance of a solitary ulcerated mammary tumor in an adult cat diagnosed by histopathology as an adenocarcinoma.

CLINICAL FEATURES

In contrast to canine mammary tumors, the vast majority (80% to 96%) of feline mammary masses are malignant, with most diagnosed as adenocarcinomas (tubular, papillary, and solid types). Less common malignant lesions include SCCs, soft tissue sarcomas, mucinous carcinomas, complex and mixed carcinomas, and inflammatory mammary carcinomas.* Cats are typically presented for palpable nodules of single or multiple mammary glands detected by the owner or found incidentally during routine physical examination. More than half of affected cats have multiple gland involvement.[34] Mammary tumors in cats may remain undetected until they become large, fixed, and ulcerated and involve multiple mammary glands or local lymph nodes (Figure 28-4).[11,12] Thus mammary carcinomas are often in an advanced state at the time of examination. If pulmonary metastatic disease is present, cats may present with acute dyspnea as a result of malignant pleural effusion, often containing exfoliating malignant cells.[27,34]

Feline fibroepithelial hyperplasia, a benign hypertrophy of the mammary glands, should not be confused with malignant mammary neoplasms. Other terms for this condition include *mammary fibroadenomatosis, pericanalicular fibroadenoma, benign mammary hypertrophy,* and *mammary adenomatosis.* Unlikely mammary carcinomas, which are less common in males, fibroepithelial hyperplasia is seen in both sexes. The condition is seen most typically in young cats shortly after a silent estrus or after chronic exogenous progestins. One or more glands may be enlarged, with occasional severe bilateral

*References 1-3, 10-12, 21, 24, 27, 29, 34.

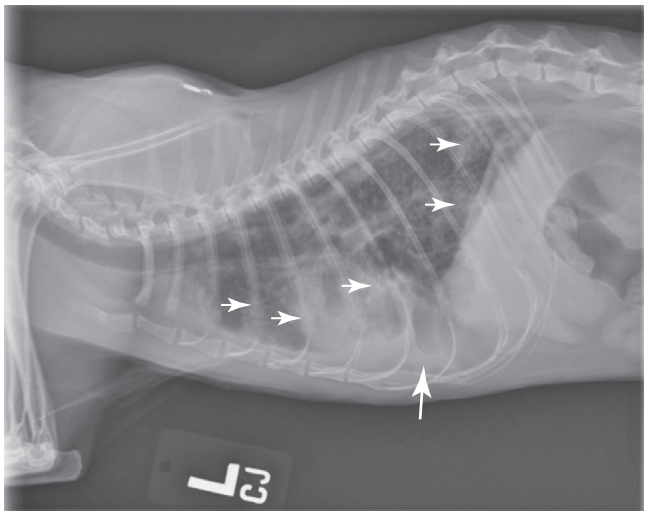

FIGURE 28-5 Left lateral thoracic radiograph from a 12-year-old domestic shorthair with metastatic mammary carcinoma. Note the diffuse interstitial to nodular metastatic pattern *(small arrows)* along with malignant pleural effusion *(large arrow)*.

TABLE 28-3 Modified World Health Organization (WHO) Staging System for Classification of Feline Mammary Tumors

T = PRIMARY TUMOR SIZE			
T_1	<2 cm maximum diameter		
T_2	2-3 cm maximum diameter		
T_3	>3 cm maximum diameter		
N = REGIONAL LYMPH NODE INVOLVEMENT			
N_0	No histologic/cytologic evidence of metastasis		
N_1	Histologic / cytologic evidence of metastasis		
M = DISTAL METASTASIS			
M_0	No evidence of metastasis		
M_1	Evidence of metastasis		
STAGES			
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III	T_{1-2} T_3	N_1 N_{0-1}	M_0 M_0
IV	Any T	Any N	M_1

enlargement noted. The affected glands are often traumatized, leading to secondary ulceration, necrosis, and discomfort. Benign feline fibroepithelial hyperplasia is treated by removing hormonal exposures of exogenous progestin therapy or performing ovariohysterectomy. It may take several months for mammary lesions to resolve.[1,12,27,34] More information on treatment of this condition is found in Chapter 40.

DIAGNOSIS AND STAGING

Because feline mammary tumors are often malignant, thorough evaluation of cats with mammary tumors is prudent to confirm diagnosis and, if malignancy is confirmed, to establish clinical stage for prognostication. Evaluation should include CBC, serum biochemistry profile and urinalysis, and evaluation of the primary tumor, regional lymph nodes, and distant metastatic sites (particularly the thoracic cavity). The primary tumor(s) should be assessed for number, site, size, consistency, ulceration, fixation to skin or abdominal wall, and nipple discharge if present. Local lymph nodes should be carefully palpated with any identified nodes aspirated or biopsied. Three-view thoracic radiographs (right lateral, left lateral, and ventrodorsal views) are vital to assess for pulmonary, lymph node, and pleural metastatic disease. Mammary tumor pulmonary metastases appear as interstitial densities ranging from small and indistinct to large and discrete nodules and may be accompanied by miliary pleural lesions with or without pleural effusion (Figure 28-5). Reported metastatic rates for feline mammary carcinomas range from 25% to 100%, with the most common sites being lungs and draining lymph nodes (axillary, inguinal, sternal).[11,12,33] Metastasis to other organs or body tissues is less common, with involvement of the liver, spleen, kidney, adrenal gland, peritoneal surface, heart, and bone reported.[3,27] A literature review of 799 cats with malignant mammary tumors found extraskeletal metastases in 338 cases. Skeletal metastasis was rare in cats compared with breast cancer in humans and mammary carcinoma in dogs.[33]

Biopsy of the mammary lesion is required for histopathologic confirmation of malignancy. Samples may be obtained before surgery by incisional biopsy or at the time of definitive surgery by excisional biopsy. Cytologic examination using fine-needle aspiration of mammary lesions in cats may confirm an epithelial neoplasm but will not distinguish reliably between benign and malignant tumors. Cytology may be helpful in ruling out nonmammary cutaneous or subcutaneous neoplasms such as mast cell tumors. Cytology is also indicated to assess suspected lymph node metastasis or malignant pleural effusions.[11,12]

Staging of feline mammary tumors is based on the modified WHO scheme first established in 1980 that assesses primary tumor size, lymph node involvement, and evidence of distant metastasis (Table 28-3).[12,34]

TREATMENT

Surgery

Surgery remains the most widely accepted primary treatment modality for feline mammary carcinomas; however, it is usually not curative. Surgery can be considered alone or, more commonly, in combination with adjuvant chemotherapy. Unilateral or bilateral (staged 2 weeks apart) radical chain mastectomies are generally recommended. Complete mastectomies are associated with decreased rate of local recurrence but do not have a significant effect on overall survival rates. The cat, unlike the dog, has four pairs of mammary glands: two cranial (thoracic) and two caudal (abdominal). The cranial glands drain to axillary and sternal lymph nodes, whereas the caudal glands drain to the inguinal nodes. The inguinal node should always be removed if the caudal mammary gland is affected. Excision of the axillary lymph node should be attempted only if enlarged and tumor involvement is confirmed on cytology because prophylactic removal of axillary lymph nodes can create significant subcutaneous dead space and is unlikely to have a therapeutic benefit.[7,11,12,25,34] Malignant mammary tumors in the cat often have lymphatic or vascular invasion, and therefore principles of surgical oncology must be observed, including early vessel ligation, gentle tumor tissue handling, *en bloc* resection of tumor, and copious flushing of the resulting surgical bed to help remove neoplastic cells.[7] The entire mammary chain should be submitted for histologic examination for tissue grading and assessment of margins. The role of ovariohysterectomy in the management of malignant mammary tumors is controversial. No impact of concurrent ovariohysterectomy with mastectomy has been demonstrated on survival rates, but some authors continue to recommend the practice to remove hormonal stimulation of the tumor.[3,9,30]

Chemotherapy

Chemotherapy is generally recommended as adjuvant therapy; however, there are no well-controlled large-scale studies documenting its role in the management of feline mammary gland tumors. Doxorubicin-based protocols are the most frequently reported, but protocols and efficacy vary among studies. Doxorubicin and cyclophosphamide combination therapy has been described, with short-term measurable responses observed in approximately half of cats with metastatic or nonresectable local disease (stage III or IV).[16,20] Retrospective analysis of single-agent doxorubicin in 67 cats (1 mg/kg intravenously every 21 days for five planned treatments) given postoperatively starting at the time of suture removal resulted in a MST of 448 days, with 1-, 2-, and 5-year survival rates at 58.9%, 37.2%, and 16.7%, respectively.[26] Doxorubicin should be used with care in cats because of the risk of nephrotoxicity. Mitoxantrone may be a suitable alternative for cats with compromised renal function. In an unpublished randomized prospective trial comparing mitoxantrone (6 mg/m^2 intravenously every 21 days for four doses) to doxorubicin (20 mg/m^2 intravenously every 21 days for four doses) for adjuvant therapy of feline mammary tumors after unilateral or bilateral radical mastectomy, no significant difference in MST or metastasis-free interval was observed between the two groups (Carolyn Henry, personal communication). MST was 747 days for mitoxantrone-treated cats and 484 days for doxorubicin-treated cats.[11-13]

Radiation

The role of radiation therapy is not well established for feline mammary tumors and is not used routinely as primary therapy. There is no evidence in current published literature supporting its efficacy or influence on survival for cats with mammary tumors. Anecdotally, according to the author's experience, hypofractionated radiation therapy in conjunction with concurrent chemotherapy may play a palliative role in inoperable local disease, with clinical responses observed.

PROGNOSIS

Average survival time between detection of primary tumor and death in untreated cats is 10 to 12 months.[8] Prognosis for malignant mammary tumors in male cats is comparable to that for female cats.[1]

Tumor size is the single most important and reliable prognostic factor in feline mammary cancer. In one study of 39 cats with mammary adenocarcinoma, a MST of 12 months for tumors larger than 3 cm was reported, compared with a MST of 21 months for tumors smaller than 3 cm after surgical excision only.[32] Prognosis for cats treated with combination surgery and adjuvant chemotherapy was discussed earlier. Other negative prognostic factors include increased WHO stage (lymph node or distant metastasis), lymphatic invasion, or immunohistochemical markers such as high AgNOR count or Ki-67 index greater than 25.2.* Histologic diagnosis is also prognostic; cats with complex carcinomas have a more favorable prognosis, with a reported MST of 32.6 months compared with 15.5 months for other mammary carcinomas. Inflammatory mammary carcinomas in cats, as in dogs, carry a poor prognosis, with rapid onset of clinical signs and euthanasia between 10 and 45 days after diagnosis.[29]

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PARANEOPLASTIC SYNDROMES

Chamisa Herrera

A paraneoplastic syndrome (PNS) is a phenomenon by which cancer cells cause a disease that is not due to the physical presence of the tumor or its metastasis. This is most often by secretion of cytokines or hormones that have some effect on body systems distant to the tumor. In cats there are a unique set of PNSs of which the veterinary clinician should be aware, including the dermatologic syndromes associated with pancreatic and thymic tumors. There are also PNSs shared among species, such as hypercalcemia and anemia. Early detection of a PNS can alert the clinician to the need for a cancer workup, including a CBC, biochemical profile, urinalysis, FeLV and FIV serology, thoracic radiographs, and abdominal imaging.

It is important to recognize that PNSs may occur before any other signs of cancer, and they may also serve as a sentinel for return of cancer in patients believed to be in remission. For this reason, if a PNS is suspected, the cat should be thoroughly screened for cancer and should be closely monitored for return of the syndrome once the cancer is in remission. Some PNSs are related to only one or a few types of neoplasia, and their presence can help narrow the differential list. PNSs can also serve as the main source of morbidity in the feline patient. When responsible for decreasing quality of life, a PNS may necessitate prioritizing symptomatic treatment before the cancer itself can be addressed.

Documented feline PNSs, their differentials, and their treatments are discussed in the subsequent sections. The

reader is directed to a veterinary oncology textbook for documented canine PNSs. There is crossover in the syndromes associated with cancer in both dogs and cats. As yet undocumented PNSs in cats could recapitulate those syndromes documented in dogs.

DERMATOLOGIC MANIFESTATIONS

Feline Paraneoplastic Alopecia

Feline paraneoplastic alopecia (FPA) is a syndrome that is unique to the cat and has been associated with pancreatic, bile duct, and hepatocellular carcinomas.[32,55,69] Cats with FPA present with a nonpruritic bilaterally symmetric progressive alopecia of the ventral thorax and abdomen, limbs, and perineum.[92] The foot pads can also be involved and appear dry and crusted.[98] FPA is unique in that the skin appears thin and glistening, devoid of elasticity, and the hairs are easily epilated (Figure 28-6).[69] On histopathologic examination, findings consistent with FPA include a nonscarring alopecia with follicular telogenization, miniaturization, and atrophy.[97] The exact mechanism of alopecia is unknown, although it has been proposed that hypoproteinemia or deficiencies in biotin, zinc, or fatty acids may be responsible for the skin lesions.[32] Resolution of the alopecia has been reported with surgical removal of the tumor,[92] but FPA usually appears late in the course of malignancy. If surgical resection of the primary tumor is not possible, the prognosis is usually poor. Noncancerous differentials for alopecia include dermatophytosis, ectoparasites, demodecosis, hyperthyroidism, and hyperadrenocorticism.

It is important to note that in the workup of a cat with alopecia, the finding of pruritus or *Malassezia* infection does not rule out FPA alopecia. In fact, a retrospective study of feline skin biopsies with *Malassezia*-associated dermatitis found that 7 out of 15 cases had dermatopathologic findings consistent with FPA.[58]

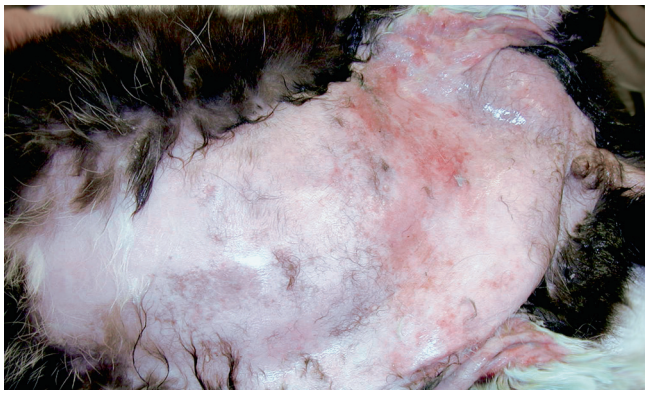

FIGURE 28-6 Abdomen of a cat with feline paraneoplastic alopecia. The entire abdomen is alopecic and the underlying skin is thin and glistening, which is typical of this syndrome. *(From Hnilica KA, editor: Small animal dermatology, a color atlas and therapeutic guide, ed 3, St Louis, 2011, Saunders.)*

Thymoma-Associated Exfoliative Dermatitis

Thymoma-associated exfoliative dermatitis is a rare PNS that has been described in cats diagnosed with mediastinal thymoma. The disease is characterized by a mild erythema of the head and pinnae that progresses to a nonpruritic generalized exfoliative dermatitis.[97] Most cats demonstrate generalized desquamation, alopecia on the body, and multifocal crusts, particularly on the head.[77] Differentials for this form of dermatitis include systemic lupus erythematosus, drug eruptions, epitheliotropic T-cell lymphoma, erythema multiforme, cheyletiellosis, demodecosis, *Malassezia* dermatitis, dermatophytosis, FeLV/FIV dermatitis, parapsoriasis, and sebaceous adenitis.[77] Histopathology of full-thickness skin lesions is helpful for diagnosis and shows perkeratotic hyperkeratosis with lymphocytic interface dermatitis.[86,88] The pathophysiology of thymoma-associated exfoliative dermatitis has not been completely elucidated; however, one theory is that an immune-mediated process directed against the tumor is occurring. This hypothesis is supported by the fact that the interface dermatitis is composed predominately of CD3+ lymphocytes.[77] The prognosis for feline thymoma and associated dermatitis is good with excision of the primary tumor, with a 1-year survival rate approaching 90%.[109]

Another PNS that has been documented in cats with thymoma is myasthenia gravis, which in a recent report occurred along with thymoma-associated dermatitis in a single cat.[86]

Cutaneous Necrosis of the Hindfeet

Symmetric cutaneous necrosis of the hindfeet has been described in a single cat with multicentric lymphoma as a presumed PNS. In this case the cat had necrosis of the hindfeet, but there were no neoplastic cells present on histopathology of this lesion, which is suggestive of a PNS.[1] Paraneoplastic digital necrosis has been described in humans with multiple malignancies, and there may be crossover between species. One hypothesis for the pathogenesis of this lesion is local or systemic vasculitis secondary to circulating tumor antigens.[11,39,72]

HEMATOLOGIC ALTERATIONS

Hyperglobulinemia

A hyperglobulinemia is an increase in serum proteins other than albumin. In cats PNSs resulting in hyperglobulinemia are rare and include multiple myeloma,

plasmacytoma, and lymphoma.[6,23,93] The primary mechanism of paraneoplastic hyperglobulinemia is production of excess gammaglobulin(s) by the tumor. Serum protein electrophoresis can be used to differentiate polyclonal from monoclonal gammopathies.[93] Monoclonal gammopathies are rare and, when observed in cats, are most often associated with neoplasia.[50,93] Other differentials for hyperglobulinemia include chronic infectious diseases such as feline infectious peritonitis, FeLV, FIV, inflammatory bowel disease, fungal disease, tick-borne disease, and immune-mediated disease (e.g., rhinitis and immune-mediated hemolytic anemia).[93]

Cats with hyperglobulinemia can develop a host of secondary complications, including infection, bleeding, and end-organ damage. Infections are common because of the decreased production of normal immunoglobulins, and antimicrobial treatment should be considered even when signs of infection are absent.[34,104] As hyperglobulinemia worsens, serum viscosity increases and leads to hyperviscosity syndrome. In humans hypergammaglobulinemia is the most common cause of hyperviscosity syndrome.[62] Increased blood viscosity results in decreased perfusion, ultimately leading to multiorgan damage. Patients with hyperviscosity syndrome present with or develop renal, retinal, or cardiac disease or neurologic abnormalities.[6,27,34] They may also have spontaneous hemorrhage with a normal platelet count, although the mechanism for this is unknown.[34] The treatment of choice for hyperglobulinemia is control of the underlying neoplasm. When immediate relief from hyperviscosity syndrome is needed, plasmapheresis can be used, including for immediate relief from congestive heart failure secondary to hyperviscosity syndrome.[9,27] Prognosis is poor if end-organ damage has occurred or the underlying neoplasm cannot be controlled.

Anemia

The causes of anemia in the feline cancer patient are numerous, including hemorrhage, immune-mediated destruction of red blood cells, and decreased red blood cell production. If a minimum database including a CBC with a manual differential, a biochemical profile, and FeLV/FIV serology do not reveal the etiology of the anemia, cancer should be considered on the differential list. The first step in differentiating causes of anemia is to determine if the anemia is regenerative (corrected reticulocyte count >60,000) or nonregenerative. A regenerative anemia is likely due to hemorrhage or hemolysis, although a hemorrhage identified early will not always be accompanied by regeneration. A common cause of a nonregenerative anemia is inflammatory disease, but such an anemia can also be attributed to decreased erythropoietin (EPO) production or bone marrow pathology. Immune-mediated destruction of red blood cells can result in either a regenerative or nonregenerative anemia.[105] In cats retroviral infection commonly causes cytopenias of various cell lines, including red blood cells, neutrophils, and platelets. A negative FeLV antigen test is a reliable means for ruling out FeLV infection as a cause of cytopenias, with only approximately 5% of cats harboring latent infections testing negative on antigen tests and positive on bone marrow polymerase chain reaction.[91]

Anemia associated with cancer can be secondary to most of the aforementioned mechanisms, making anemia difficult to definitively pinpoint as a PNS. For example, hemorrhage can occur secondary to a bleeding tumor in the gastrointestinal tract, the nasal cavity, or the thoracic or abdominal cavities. Although hemoperitoneum in cats is rare, almost half of cats with that diagnosis in one study had intraabdominal neoplasia, most often hemangiosarcoma.[19] Hemolysis of red blood cells with cancer is secondary to production of anti-erythrocyte antibodies. This has been documented in lymphoma in the cat.[44,52] Renal failure, and therefore decreased EPO production, can be secondary to a primary renal tumor or a tumor that is metastatic to the renal parenchyma or caused by renal hypoxia secondary to a neoplastic embolism. Cancer itself can serve as a chronic source of inflammation and lead to anemia of inflammatory disease (AID). The mechanisms of AID are multifactorial and include decreased red blood cell survival, iron sequestration, and insufficient EPO production or bone marrow response (or both).[68] One of the main mediators of AID is believed to be hepcidin, which is a hormone responsible for iron homeostasis that is upregulated in inflammatory conditions in response to interleukin-6. This upregulation of hepcidin is thought to deprive infectious agents of iron but also reduces iron stores necessary for erythropoiesis.[17,61,87,106]

A unique mechanism that can contribute to anemia in cancer is erythrophagocytosis of red blood cells by the tumor. This has been documented in an extranodal T-cell lymphoma, histiocytic sarcoma, mast cell tumors, and multiple myeloma in the cat.[13,40,54,103]

The prognosis for anemia associated with cancer depends on the underlying mechanism, the degree of anemia, and the animal's response to symptomatic treatment of the anemia or treatment of the underlying neoplasia.

Polycythemia

Polycythemia is another neoplastic syndrome that is more commonly described in cats than dogs, but it is rare in veterinary medicine. Diagnosis of polycythemia is uncomplicated and easily diagnosed by performing packed cell volume and total protein measurements. It is important to rule out non-neoplastic causes of polycythemia. A relative polycythemia results from

dehydration or hypovolemia, is often accompanied by high serum total protein, and will resolve with fluid therapy. An absolute polycythemia can be primary, as in polycythemia vera, or secondary to conditions such as chronic hypoxia, excessive EPO production, and cancer. Serum EPO concentrations have been used for differentiating polycythemia vera from secondary polycythemia; however, there is overlap between the two groups, and testing is not readily available.[35]

Secondary polycythemia in feline cancer patients has been documented in primary renal tumors.[37,43] Similar to hyperglobulinemia, polycythemia can result in hyperviscosity syndrome. The most common clinical signs are neurologic and include seizures and ataxia.[43,75] Paraneoplastic polycythemia is thought to arise from renal hypoxia, production of EPO by the tumor, or both.[22] In patients with an absolute secondary polycythemia and a hematocrit greater than 65%, symptomatic treatment is achieved by therapeutic phlebotomy.[28] Leeching as an initial treatment for feline patients for whom phlebotomy proves impossible has also been documented.[66]

Prognosis is variable. Resolution of polycythemia has been achieved with nephrectomy of the affected kidney, although this requires unilateral disease and adequate function of the contralateral kidney.[43]

Thrombocytopenia and Disseminated Intravascular Coagulation

Thrombocytopenia is conservatively defined as a platelet count of less than 200,000/μL and frequently occurs in various disease states. One of the most common reasons for this finding is laboratory error because of the tendency of feline platelets to aggregate and be misread by automated systems.[67] The first step when thrombocytopenia is suspected in a cat is to have a manual platelet count performed to rule out platelet aggregation as a cause.

Differentials for a true thrombocytopenia include infectious disease (e.g., FeLV, FIV, feline infectious peritonitis, other infectious and inflammatory causes), neoplasia (e.g., leukemia, lymphoma, hemangiosarcoma), cardiac disease, and primary immune-mediated disease, with infectious disease and neoplasia within the bone marrow being the most common causes.[41] The pathophysiologic mechanisms of thrombocytopenia include destruction, decreased production, consumption, and sequestration within the spleen. Many of these mechanisms may also play a role in thrombocytopenia associated with cancer. For example, platelet-bound antibodies have been demonstrated in cats with immune-mediated thrombocytopenia secondary to lymphoma.[44] Cancer can also cause thrombocytopenia as a result of decreased production secondary to bone marrow invasion, sequestration of platelets within the spleen, and consumption resulting from disseminated intravascular coagulation (DIC). When DIC occurs in cats, neoplasia is often an underlying etiology and survival rates are poor.[25]

Thrombocytopenia can result in spontaneous hemorrhage when platelet numbers fall below 30,000/μL. Prognosis for thrombocytopenia secondary to a malignancy is variable and depends on the underlying mechanism leading to thrombocytopenia, the degree of thrombocytopenia, and the responsiveness of the tumor to antineoplastic therapies.

Eosinophilia

Dramatic increases in peripheral eosinophil counts can occur for a variety of reasons in the cat, including parasitism, allergic diseases, hypereosinophilic syndrome, and eosinophilic leukemia.[16,18,108] Eosinophilia can also occur as a PNS and in cats has been documented in lymphoma, mast cell tumors, and transitional cell carcinoma.[4,71,82] Lymphoma and various other sarcomas and carcinomas have also been documented as causes of paraneoplastic eosinophilia in dogs and humans.[26,49,89,99,100]

The mechanism of eosinophilia is believed to be production of cytokines important in eosinophil proliferation, particularly interleukin-3, interleukin-5, granulocyte macrophage colony-stimulating factor, and potentially some other eosinophilotactic factors produced by the tumor.[3,82,94,102] Diagnosis of paraneoplastic eosinophilia relies on ruling out other causes of eosinophilia, including hypereosinophilic syndrome and eosinophilic leukemia, or seeing resolution of the eosinophilia with treatment of the underlying neoplasia. Prognosis for paraneoplastic eosinophilia in cats is not well studied. In humans peripheral eosinophilia in association with a tumor usually carries a poor prognosis—not because of the eosinophils themselves but because this is associated with widespread metastasis of the underlying malignancy.[53]

ENDOCRINOLOGIC MANIFESTATIONS

Hypercalcemia of Malignancy

Hypercalcemia of malignancy (HM) is one of the most recognized paraneoplastic syndromes in veterinary medicine; however, it is less commonly reported in the cat than in the dog.[24] In cats the most common tumors resulting in HM are lymphoma and SCC.[78] Other tumors reported to cause HM in cats include leukemia, fibrosarcoma, osteosarcoma, multiple myeloma, and various carcinomas, particularly bronchogenic adenocarcinoma.[8,15,70,78,80] The distribution of clinical signs in the cat is unique, with the most common being anorexia and lethargy followed by gastrointestinal signs, polyuria and polydipsia, urinary signs, and neurologic signs.[78] Hypercalcemia commonly causes significant morbidity

when elevations are profound, including renal failure, arrhythmias, seizures, and coma. The most common mechanism of HM is thought to be production of parathyroid hormone–related peptide (PTH-rp) by the tumor; however, other mechanisms of HM include skeletal metastasis and diffuse osteolysis caused by production of humoral products produced by the tumor.[78] The most common non-neoplastic cause of hypercalcemia is renal failure.[78] Other causes include idiopathic hypercalcemia, vitamin D toxicosis, and granulomatous disease.[38,60,63,73] Primary hyperparathyroidism has been reported in cats and, although extremely rare, also results in hypercalcemia.[20]

In general, hypercalcemia is more profound when related to a malignant process than hypercalcemia associated with non-neoplastic diseases, and may be indicative of, although not definitive for, the underlying process.[78] Diagnosis relies on ruling out other causes of hypercalcemia. In the past a PTH-rp assay could be performed to look for production of parathyroid hormone–related peptide production by the tumor,[8] but this diagnostic tool recently became unavailable. The best treatment option for HM is to treat the underlying neoplasia. When this is not possible or when the hypercalcemia itself is causing significant morbidity (e.g., renal failure, arrhythmias, seizures), symptomatic treatment should be aggressive and immediate. Initial treatment is fluid diuresis with a calcium-poor solution (0.9% NaCl).[79] Furosemide, prednisone, salmon calcitonin, and bisphosphonates can also be used to decrease serum calcium.[64,79,107] Use of furosemide should be limited to patients that are well hydrated. In the patient with hypercalcemia of unknown origin, treatment with prednisone can make diagnosis of lymphoma difficult by inducing remission and can also cause chemotherapeutic resistance. For this reason steroid treatment of hypercalcemia should not be instituted until lymphoma has been ruled out. In cases of severe hypercalcemia that require management without a cancer diagnosis, administration of bisphosphonates is preferred. Prognosis for patients with HM is considered poor, regardless of the underlying neoplasia.

Hypoglycemia

Hypoglycemia, defined as a blood glucose below 70 mg/dL, has been documented to occur as a PNS in both cats and dogs suffering from cancer. The mechanisms of paraneoplastic hypoglycemia are variable, but production of insulin by an insulinoma is probably the most common.[46] Other mechanisms of cancer-associated hypoglycemia include liver failure secondary to metastasis and production of insulin-like growth factor II by the tumor.[76] In the cat tumor types that have been shown to cause hypoglycemia include insulinoma, lymphoma, and hepatoma.[30,36,45,95] In dogs tumors associated with hypoglycemia include hepatocellular carcinoma, leiomyosarcoma, hemangiosarcoma, melanoma, and various carcinomas[5,51,76] and could theoretically also cause hypoglycemia in a similarly affected cat. Clinical signs associated with hypoglycemia include weakness, lethargy, muscle twitching, and seizures. Neurologic complications might become irreversible with chronic hypoglycemia secondary to insulinoma, even after treatment and normalization of glucose levels.[45] A diagnosis of paraneoplastic hypoglycemia should be considered when an adult cat presents with a persistent hypoglycemia and other causes have been ruled out. Non-neoplastic differentials include sepsis, hepatic disease, hypoadrenocorticism, portosystemic shunt, and insulin overdose. Diagnosis of an insulinoma can be made when a persistent hypoglycemia with concurrent normal to increased serum insulin concentrations are present. Diagnosis of other causes of paraneoplastic hypoglycemia is likely to be presumptive or require biopsy and immunohistochemical staining to demonstrate the underlying mechanism. Alternatively, documenting glycemic control with treatment of the tumor supports the diagnosis of this PNS. Prognosis for an insulinoma in cats is guarded because of the metastatic nature of the disease; however, prolonged survival times have been documented with surgical excision when no metastases were present.[33] Prognosis with other causes of paraneoplastic hypoglycemia varies depending on the tumor type and mechanism by which the tumor induces glucose dysregulation.

NEUROMUSCULAR MANIFESTATIONS

Peripheral Neuropathy

The characteristic physical examination findings associated with a peripheral neuropathy include hyporeflexia, motor or sensory involvement (or both), and occasionally autonomic dysfunction. There are numerous etiologies of peripheral neuropathies in cats, including inherited disorders, endocrine diseases (e.g., diabetes mellitus, hyperthyroidism), infectious disease (FeLV, FIV), nutritional disorders (e.g., phenylalanine deficiency, tyrosine deficiency), toxins (e.g., organophosphates, carbamates, heavy metals), drugs (e.g., aminoglycosides, vincristine), neoplastic invasion of a tumor into a nerve, and paraneoplastic peripheral neuropathies (PPNs).[14] In cats a single case report of PPN has been described in a cat with renal lymphoma.[14] Muscle and nerve sections from the cat showed demyelination, axonal degeneration, and muscle denervation.[14] No neoplastic cells were observed in the affected muscle or nerve biopsies, which is consistent with a PPN.[14] Although this is the first described case in a cat, several tumors have been implicated in PPN in dogs,

including insulinoma, lymphoma, primary lung tumors, multiple myeloma, mammary adenocarcinoma, and melanoma.[10,56,74,101] Polyneuropathy has been reported in various neoplasms in human-medicine literature as well.[31] The underlying cause is thought to be autoimmunity through the production of onconeural antibodies by the tumor.[59,90] These antibodies can be directed at any part of the peripheral nerve, including the cell body, axon, myelin sheath, and presynaptic region. Treatment of PPN is removal or treatment of the underlying neoplasm and supportive care; however, given the presumed immune-mediated component, immunosuppressive medications may be another treatment modality to consider.

Myasthenia Gravis

Acquired myasthenia gravis is an immune-mediated neuromuscular disorder by which antibodies alter, block, or destroy acetylcholine receptors (AChRs), resulting in muscle weakness and fatigue. In cats myasthenia gravis usually results in generalized weakness, although focal signs such as dysphagia and megaesophagus can also be seen.[84] Other clinical signs may include gait abnormalities, voice change, neck ventroflexion, and regurgitation.[42] Approximately 25% of cats in a study of risk factors for myasthenia gravis had a cranial mediastinal mass, most of which were thymomas.[84] This is very different from myasthenia in dogs, in which only about 3% of cases have a mediastinal mass.[85] Production of onconeural antibodies by the tumor is the likely mechanism of AChR blockade and is by definition a type of PNS. Definitive diagnosis of myasthenia gravis can be achieved by demonstrating AChR antibodies by immunoprecipitation radioimmunoassay. A feline-specific immunoprecipitation radioimmunoassay should be used, although there is some cross-reactivity between species.[83] Treatment for paraneoplastic myasthenia gravis in cats is not well described, although removal of the tumor has been shown to cause complete resolution of focal myasthenia gravis in a dog.[48] Acetylcholine esterase inhibitors and antiinflammatory doses of corticosteroids may also be useful in the absence of aspiration pneumonia.[81]

CANCER CACHEXIA AND ANOREXIA

Some cancer patients experience anorexia or weight loss secondary to treatment or because of the location of the tumor (gastrointestinal), which is beyond the scope of this discussion and occurs by a mechanism likely to be different from that of cancer cachexia. Those patients who involuntarily lose weight before diagnosis or independent of treatment of their disease have the PNS termed *cancer cachexia*. Cancer cachexia can occur with or without anorexia, although weight loss is often seen despite normal caloric intake.[7] The mechanisms of this disease are multifactorial and poorly understood but result in weight loss through the depletion of lean muscle mass and adipose tissue, which differentiates it from malnutrition.[65] The true prevalence of cachexia in human cancer patients is unknown, and the literature reveals huge variability, ranging from less than 3% to 87% of cancer patients, depending on the definition, type of cancer, and stage of disease used in each study.[21,29] One well-recognized phenomenon in human oncology patients is that cancer cachexia is associated with a higher incidence of treatment failure and reduced survival.[21,57] Production of cytokines and hormones by the tumor or host immune system are thought to contribute to cachexia and anorexia by altering appetite, increasing resting energy expenditure, increasing lipolysis, altering fat metabolism, increasing protein catabolism, and depressing protein synthesis.[96] Excessive glucose use by tumor cells may also play a role in weight loss.[12] A single study investigating the prevalence and prognostic significance of weight loss and body condition score (BCS) has been reported in cats. This study evaluated cats with various tumor types and found that 60% had reduced fat mass and 91% had reduced muscle mass. They also found that patients with a BCS below 5 (on a 9-point scale) had an MST of 3.3 months compared with 16.7 months for cats with a BCS of 5 or above.[2] Based on this information, physical examination monitoring (including estimates of muscle and fat mass), as well as recording of BCS and trends in weight, should occur in all cats with cancer. This information may provide prognostic data and serve as a guide for attempted intervention. Because cancer cachexia is not solely caused by inadequate caloric intake, treatment aimed at increasing caloric intake may not be effective. Studies in humans have investigated various drugs for treatment of cancer cachexia and anorexia, including appetite stimulants, 5-HT_3 antagonists, and cyclooxygenase-2 inhibitors, none of which have proved successful.[47] With continued research and understanding of the mechanisms involved in cancer cachexia and anorexia, new pharmacologic interventions may become available.

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PALLIATIVE CARE

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The term *palliative care* refers to medical therapy primarily administered to treat the symptoms of cancer, as opposed to directly treating the cancer itself. The ultimate goal is to maintain or improve quality of life. Palliative care is commonly used for advanced stage and terminal cancer alone or in combination with standard cancer therapies. Palliative care is *not* synonymous with giving up. Unfortunately, in very advanced-stage disease traditional cancer therapy may in fact worsen the pet's quality of life and offer little chance of providing significant benefit to the patient. Conversely, palliative care still improves patient comfort levels, even when prolongation of life is not possible. Compassionate and humane palliative treatment for the pet also contributes to client satisfaction.

The primary clinical signs associated with advanced feline cancer include physical and mechanical dysfunction (e.g., dysphagia, cramping, obstipation, dyspnea) and concerns secondary to metabolic or paraneoplastic processes (e.g., anorexia, nausea, fever, anemia, cachexia, and electrolyte imbalances). These problems may be exhibited as overt pain, discomfort, lack of social interaction, or anxiety, in addition to physical dysfunction.

QUALITY OF LIFE SCORE SYSTEMS

Although many feline cancers are not curable, palliation of clinical signs will improve the quality of life in most cats with cancer. This is a major concern for pet owners; quality of life is often more important than the length of life. Assessing quality of life in feline patients can be very difficult and depends on the individual cat's behavior as well as owners' perceptions. Several quality of life score systems have been proposed for cats.[3,4] Dr. Villalobos's quality of life scoring system, "HHHHHMM," incorporates measures of "*h*urt, *h*unger, *h*ygiene, *h*ydration, *h*appiness, *m*obility, and *m*ore good days than bad" and attempts to provide a more objective means for the caregiving team (client and veterinary staff) to determine appropriate intervention or euthanasia (Table 28-4).[3] The key is open communication between veterinarian and pet owner about factors that contribute to decreased quality of life, as well as monitoring relatively feline-specific behaviors such as hiding, lack of grooming, and lack of social interaction.

TABLE 28-4 The HHHHHMM Quality of Life Scale*

Score	Criterion
Hurt: 0-10	Is pain successfully managed?
Hunger: 0-10	Is the cat eating enough? Is a feeding tube required?
Hydration: 0-10	Is the cat dehydrated? Is subcutaneous fluid therapy necessary?
Hygiene: 0-10	The cat should be groomed and cleaned regularly; avoid pressure sores and keep all wounds clean.
Happiness: 0-10	Does the cat express interest in its environment? Is it responsive to family, toys, other pets, and so forth?
Mobility: 0-10	Can the cat move without assistance? Are neurologic signs or pain impairing mobility?
More good days than bad: 0-10	When bad days outnumber good days, quality of life may be compromised. When a healthy human-animal bond is no longer possible, the owner should be aware that the end is near. Euthanasia may be necessary to prevent further pain and suffering.
Total =	A total of 35 points or more is acceptable for good quality of life.

*Score patients on a scale of 1 (poor) to 10 (best).
Adapted from Myers F: Palliative care: end of life "pawspice" care. In Villalobos A, Kaplan L, editors: *Canine and feline geriatric oncology: honoring the human-animal bond,* Ames, Iowa, 2007, Wiley-Blackwell.

ANALGESIA

Pain control is an important aspect of cancer care in feline patients. Pain may be visceral (e.g., gastrointestinal lymphoma), somatic (e.g., jaw pain with oral tumor), or neuropathic (e.g., extension of a soft tissue sarcoma along nerve fibers). If pain is suspected despite a lack of apparent clinical signs, analgesic intervention may function as a diagnostic test for pain as well as a directed

therapy. To address cancer-related pain in cats, the veterinarian should consider several strategies,[2] including the following:

1. Direct treatment of painful site: Bulky tumors or those involving bone may be amenable to direct therapy such as cytoreductive surgery or palliative (coarse fraction) radiation therapy. Intravenous aminobisphosphonates (e.g., pamidronate, zoledronate) may also be useful for malignant bone lysis, such as a primary bone tumor (e.g., osteosarcoma), metastatic bone tumor (e.g., digital metastasis of primary lung tumor), and local tissue invasion (e.g., oral SCC, injection-site sarcoma). These drugs are potentially nephrotoxic and should be used with caution, especially in conjunction with other analgesics and chemotherapeutics. In some cases systemic chemotherapy may also be effective to palliate clinical signs. The treatment goals may focus on reduction of inflammation or pain, reduction in tumor volume, or slowing of growth to improve clinical signs rather than cure of the disease.
2. Remove or reduce contributing environmental factors: Care should be taken to modify the cat's home environment for maximal comfort. Cats with intranasal tumors may benefit from a room humidifier. To help cats with limited mobility, items such as litter boxes, food, and water bowls should be easily accessible (e.g., at floor level). The owner should minimize the necessity of high jumps and stairs and provide safe, comfortable, and accessible private resting areas away from other household pets that might contribute to patient stress. For cats with oral tumors, moistened or canned food and soft toys should be used.
3. Local analgesic techniques: Although rarely practical for long-term use, local analgesic options (e.g., nerve blocks, topical analgesics, local analgesic patches) may be considered in certain cases.
4. Systemic analgesia: This is the most common form of clinical pain management in cats and often includes nonsteroidal antiinflammatory drugs and opioids. Patients with cancer may be at increased risk of organ toxicity as a sequela of the tumor, primary treatment, or supportive medications. Cats are more sensitive than dogs to the toxic side effects of many analgesics, and most feline cancer patients are also geriatric. Contraindications and interactions with other medications should be taken into consideration, particularly with drugs that are potentially nephrotoxic or hepatotoxic. Some chemotherapy agents may potentiate organ toxicity. For example, doxorubicin and carboplatin are commonly used chemotherapy agents that are potentially nephrotoxic. Sedation and anesthesia should be minimized but may be necessary for procedures such as radiation therapy or feeding tube placement; this may place additional stress on kidneys and other organs.
5. Complementary therapies: Physical therapy and rehabilitation techniques such as physical manipulation are poorly tolerated by most cats but could be considered in certain cases. Options include range-of-motion exercises, massage therapy, acupuncture, acupressure, and chiropractic care. Client instruction for home care may be more feasible than in-hospital physical therapy.

For more complete information on feline analgesia, please refer to Chapter 6.

NUTRITIONAL CARE

Nutritional care of feline cancer patients should address route of administration, optimal nutritional content, palatability, appetite stimulation, nutritional supplementation, supportive care of gastrointestinal upset, and recognition of the effects of cancer cachexia. Cancer-bearing cats are often underweight, with most exhibiting reduced fat stores and muscle mass. BCS is prognostic in cats, with average or obese cats living significantly longer than thin cats.[1]

Cancer cachexia is a poorly understood paraneoplastic process in veterinary patients. In human oncology cancer cachexia is recognized as a complex metabolic syndrome that manifests as severe weight loss, muscle wasting, and inappetence. Contributing factors include maldigestion and malabsorption as well as functional abnormalities leading to decreased nutritional intake. Examples include painful oral tumors, obstructive or malabsorptive gastrointestinal tumors, and systemic cancers that induce nausea, vomiting, and diarrhea. Metabolic and physiologic alterations are more subtle contributing factors to cachexia and may include altered nutrient metabolism (carbohydrates, protein, and fats), altered insulin response, and cytokine abnormalities. These derangements can result in severe weight loss even in the face of normal or apparent increased food intake.

Enteral feeding is always preferred because it maintains gastrointestinal epithelial health and offers safety and convenience. For short-term care of hospitalized patients, a nasogastric tube is easily managed. Esophagostomy tubes (E-tubes) are ideal for both short- and longer-term home care for patients with oral tumors or nonspecific inappetence that are not actively vomiting. E-tubes are easily placed during a short anesthesia procedure and are extremely well-tolerated by cats (see Chapter 18). Newer feline-specific E-tubes are commercially available and are appropriately sized, flexible, and

radio-opaque to optimize placement. Cats are able to eat on their own with E-tubes in place, and this provides a low-stress option for owners to administer both nutrition and medication. Another less commonly used long-term home option is a gastrostomy tube. In select cases partial parenteral or total parenteral nutrition is used in the intensive care unit for short-term support of hospitalized patients, such as after an invasive surgical procedure. Hand feeding may also encourage food intake, although assisted feeding in the form of force feeding or syringe feeding is often poorly tolerated and may lead to food aversion and bite injuries to pet owners.

The ideal diet for the feline cancer patient has yet to be determined. Given the metabolic alterations of cancer cachexia, a diet low in simple carbohydrates with moderate lipids and easily digestible protein sources is ideal. Many adult commercial cat foods meet these criteria. Because many cats may be geriatric or have chronic renal insufficiency, these medical concerns should also be taken into consideration when selecting an appropriate diet. In addition to adequate nutritional composition, palatability is a major concern. The best answer to the question, "What should I feed my cat with cancer?" is usually, "Whatever he or she will eat." Standard methods to improve palatability include trying different brands of cat food, canned cat food, or human food, such as tuna, deli meats, and cheese. Warming up the food or adding cooking liquids or milk may also improve palatability for some cats. The role of specific nutritional supplements is poorly understood in clinical feline patients. However, supplementation should be instituted as clinically indicated (e.g., vitamin B_{12} supplementation in cats with intestinal lymphoma). Specific recommendations for nutritional care of feline cancer patients can be found in Chapter 18.

Appetite stimulants are most effective in mildly affected cats or in temporary situations such as when the cat is recovering from anesthesia or surgery. Appetite stimulants may not adequately improve food intake and may have inconsistent results. Mirtazapine is a newer appetite stimulant with good efficacy in cats. Cyproheptadine may also be effective, although cyproheptadine and mirtazapine should not be used concurrently because their actions are antagonistic. In a hospital or short-term situation, oral diazepam could be administered if other oral medications are ineffective. Side effects and toxicity may occur with all these medications, and they should be prescribed with appropriate monitoring. For example, mirtazapine dose should be reduced in the presence of renal insufficiency.

Other supportive gastrointestinal medications include histamine receptor (H_2) antagonists (e.g., famotidine), coating agents such as sucralfate, and proton pump inhibitors (e.g., omeprazole) (Table 28-5). Fiber supplementation or lactulose may alleviate constipation in predisposed cats or in cases complicated by abdominal, pelvic, or intestinal discomfort. Antiemetics may be effective for nonobstructive gastrointestinal cancer or nonspecific/systemic cancers that contribute to nausea or vomiting. Some options include metoclopramide (a prokinetic and centrally acting antiemetic); 5-HT_3 receptor antagonists (ondansetron, dolasetron); and, more recently, the neurokinin-1 receptor antagonist maropitant citrate (Cerenia). Although routinely used in small animal patients, metoclopramide is less effective in cats than in dogs because of differences in CNS neurotransmitter receptors at the chemoreceptor trigger zone. Options for management of acute and chronic diarrhea in feline cancer patients include dietary modification, addition of dietary prebiotics and feline-specific probiotics, and direct medical therapy. Metronidazole is most commonly used and should be prescribed at the lowest effective dose.

Outpatient or at-home subcutaneous fluid therapy should be instituted for cats with inadequate fluid intake and those with increased risk of renal toxicity. Cats with preexisting renal insufficiency or those receiving nephrotoxic medications (e.g., nonsteroidal antiinflammatory drugs, chemotherapy agents such as doxorubicin and carboplatin) and geriatric animals undergoing procedures requiring sedation should be supported with appropriate fluid therapy.

For further information on drug therapy and fluid therapy, please refer to Chapters 4 and 5.

MISCELLANEOUS CARE

Sick cats and those with oral tumors often stop grooming, necessitating additional home care by the pet owner. Oral health concerns such as bacterial infections and malocclusion should be assessed and treated as needed. Cats undergoing systemic chemotherapy may be at increased risk of myelosuppression and susceptibility to secondary bacterial infections. Common routes of entry include the oral cavity, colon and intestinal tract, lower urinary tract, skin, and ears. Pleural effusion secondary to mediastinal lymphoma, primary or metastatic lung tumors, or carcinomatosis (microscopic tumor seeding of pleura) may decrease the cat's quality of life, and thoracocentesis can be performed as an acute palliative measure, although effusion often progresses quickly. Abdominal effusion is less likely to reduce the patient's quality of life, and therapeutic abdominocentesis should be performed only if clinically necessary to reduce losses of protein and electrolytes and minimize patient stress.

In summary, a variety of supportive and medical therapies can be instituted for feline cancer patients. The goal of palliative care is to maintain and maximize the pet's quality of life and should incorporate a whole-health approach.

TABLE 28-5 **Selected Supportive Gastrointestinal Medications in Feline Cancer Patients**

Drug	Action	Mechanism	Site of Action	Feline Dose
Famotidine (Pepcid AC)	Gastric acid reduction	Histamine H_2-receptor antagonist	Peripheral	0.5-1 mg/kg PO, SC, IV every 12 to 24 hours
Ranitidine (Zantac)	Gastric acid reduction Prokinetic	Histamine H_2-receptor antagonist	Peripheral	1-2 mg/kg PO, SC, IV every 12 hours
Omeprazole (Prilosec)	Gastric acid reduction	Proton pump inhibitor	Peripheral	0.5-1 mg/kg PO every 24 hours
Maropitant (Cerenia)	Antiemetic	NK-1 antagonist	Central Peripheral	Empirical 0.5-1 mg/kg short-term
Metoclopramide (Reglan)	Antiemetic	Dopaminergic antagonist Suspected acetylcholine sensitization?	Peripheral Central	Empirical 0.2-0.4 mg/kg PO, SC every 6-8 hours
Ondanestron (Zofran)	Antiemetic	5-HT3 serotonin antagonist	Central Peripheral	Empirical 0.1-0.5 mg/kg every 12 hours
Mirtazapine	Appetite stimulant	Noradrenergic agonist Serotonin agonist	Central	3.75 mg PO/cat every 72 hours or 1 mg/cat per day, compounded
Metronidazole (Flagyl)	Anticolitis Antidiarrheal	Antibiotic Other	Peripheral	10-15 mg/kg PO every 12 hours, short-term (3-5 days)

PO, Orally; *SC,* subcutaneously; *IV,* intravenously.

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