Angela E. Frimberger, VMD, Diplomate ACVIM (Oncology), and Antony S. Moore, BVSc, MVSc, Diplomate ACVIM (Oncology),
Veterinary Oncology Consultants, Wauchope, New South Wales, Australia

Support for the Neutropenic Cancer Patient

Treating cancer in veterinary medicine requires maintaining the highest possible quality of life for patients receiving treatment.

All chemotherapeutic drugs can cause adverse side effects; however, side effects in pets are usually not as severe as those in humans due to lower doses. Regardless, some toxicity may occur, primarily after the first dose of the chemotherapy drug and before the dose has been "individualized" for that patient; although toxicity occasionally occurs later in the course of treatment. Neutropenia is the toxicity most likely to be life-threatening, because it increases the risk for sepsis.

Neutropenia is a reduced neutrophil count, although the degree of reduction varies considerably and most neutropenic animals do not exhibit clinical signs. *Sepsis* (often used interchangeably with *septicemia*) refers to a generalized bacterial infection resulting in severe morbidity, acute clinical deterioration (*septic shock*), and possibly mortality. Sepsis is usually accompanied by fever, but severely neutropenic animals may be afebrile despite overwhelming sepsis.

Indications

Sepsis due to chemotherapy or cancer-related neutropenia is usually preventable through judicious monitoring and appropriate supportive care. To assist in early detection and seek immediate treatment, caregivers should be educated about its early clinical signs. The risk for neutropenic sepsis is less than 5% in veterinary patients, but because dogs and cats may hide clinical signs, the condition may be quite advanced when first recognized and requires prompt veterinary intervention. Timely treatment can make the difference between life and death.

Chemotherapy agents vary in their myelosuppressive potential (**Table**). Knowing the myelosuppressive potential for the chemotherapy drugs being administered and having an estimate of the time that the absolute neutrophil count (not just total white cell count) nadir—or low point—will occur, allows the veterinarian to monitor blood counts and administer prophylactic antibiotics, if that approach is chosen.

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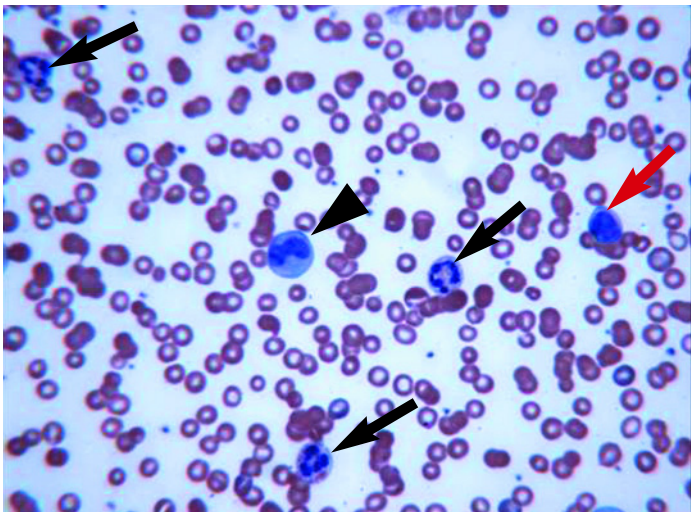
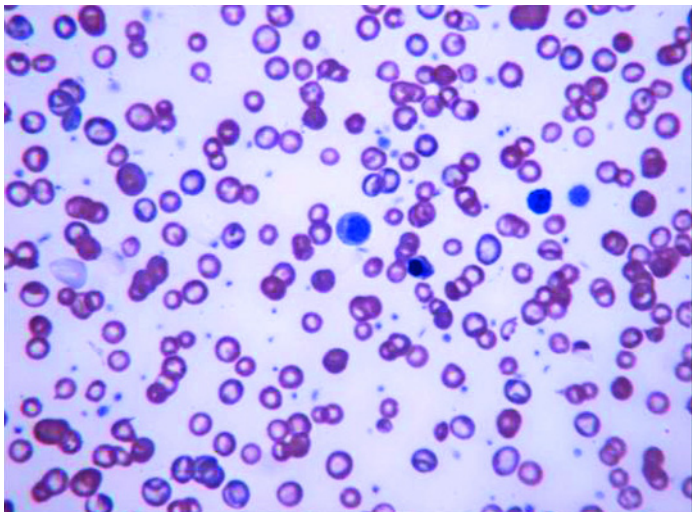


A blood smear from a normal dog. Note that 3 neutrophils (*arrows*), 1 monocyte (*arrowhead*), and 1 lymphocyte (*red arrow*) are evident on the smear.



In contrast to the first figure, this blood smear has no evident neutrophils. However, this subjective assessment should always be considered in tandem with a neutrophil count to grade the neutropenia and to plan any necessary intervention.

Photos courtesy Dr. Dennis Meyer

Myelosuppressive Effects of Chemotherapeutic Agents Used in Veterinary Medicine

Highly myelosuppressive	Moderately myelosuppressive	Mildly myelosuppressive
Doxorubicin	Melphalan	L-asparaginase*
Vinblastine	Chlorambucil	Vincristine*
Cyclophosphamide	5-fluorouracil	Bleomycin
Lomustine (CCNU)	Methotrexate	Corticosteroids
Actinomycin-D	Procarbazine	
Mitoxantrone	Cisplatin	
Carboplatin		

*More pronounced myelosuppression can occur if these 2 drugs are administered concurrently.

Assessment

The neutrophil nadir occurs 7 to 10 days after administration for most chemotherapeutics, and for consistency a CBC is done 7 days after administration to assess the risk for sepsis and whether the dosage needs to be adjusted. The aim is to have a nadir between 1000 and 3000 segmented neutrophils/µl.[1] The nadir is usually brief at the doses used in veterinary medicine, recovering to normal within 48 to 72 hours.

Some drugs may cause a delayed neutrophil nadir—for example, carboplatin may cause a nadir 2 or even 3 weeks after administration in cats and in some dogs. In addition, the return to normal levels may be further delayed, particularly in cats. ***Clinicians should check the expected nadir time and severity for each drug they use.*** They should also be familiar with factors that could cause alterations in chemotherapy drug metabolism and increase the risk for myelosuppression (eg, reduced renal clearance may exacerbate the myelosuppressive effects of carboplatin) in each species.

Course of Treatment

Prevention of Complications

When neutropenia is treated promptly and aggressively, the prognosis is fair to good, but if allowed to progress to septic shock, the prognosis deteriorates markedly. Some individuals tolerate even severe neutropenia without developing signs of illness, but there are several factors that seem to increase the risk for sepsis. Whenever possible, these risk factors must be avoided or minimized and associated problems recognized and corrected early.

One logical step is to minimize the administration of immunosuppressive drugs, especially corticosteroids, except when needed for treatment of the cancer. Risk for catheter-induced sepsis can be minimized by placing a new catheter in a new site every 2 to 3 days. Strict aseptic procedures should be used, especially with animals that are myelosuppressed. The duration of hospitalization should be limited whenever possible to reduce exposure to antibiotic-resistant bacteria.

Prophylactic antibiotic therapy is often recommended for patients receiving myelosuppressive chemotherapy as a method of reducing the risk for sepsis. The cost of prophylactic treatment must be weighed against the decreased risk for morbidity due to sepsis, as well as decreased risk for hospitalization and costs associated with it. Some oncologists recommend use of trimethoprim-sulfa (15 mg/kg PO Q 12 H) ($) as a prophylactic measure in any dog receiving a myelosuppressive agent for the first time (until the nadir neutrophil count is known). The drug is relatively inexpensive, is given orally, and has little negative effect on gastrointestinal flora. This approach has been shown to reduce morbidity and hospitalization in dogs treated with doxorubicin for osteosarcoma or lymphoma.[2] In cats, enrofloxacin (5 mg/kg PO Q 12 H) ($) or orbifloxacin (5 mg/kg PO Q 12 H) ($) can be given.

Canine recombinant G-CSF (5 µg/kg SC Q 24 H) may increase cell numbers and enhance neutrophil function. Human recombinant G-CSF is commercially available ($$$$$); however, long-term use may induce antibody formation to the protein, which can cause a paradoxic neutropenia. Whether these drugs improve outcome in patients that already have neutropenia and therefore already have maximal stimulation of their endogenous G-CSF is controversial. Most neutropenic patients recover rapidly without G-CSF administration, and the rapid recovery observed after exogenous administration may be due to endogenous CSFs rather than the treatment.

In human patients, trials in febrile neutropenic patients have provided conflicting results. Although neutrophil recovery times are faster with CSF and antibiotic therapy, duration of hospitalization may not be reduced except in patients receiving *less myelosuppressive* chemotherapy treatments.[3] It is our opinion that G-CSF has a role in prevention of severe myelosuppression after an inadvertent overdose of a myelosuppressive chemotherapy agent. In that situation, treatment should be started within 48 hours (but *not* before 24 hours) of the overdose. The use of human recombinant CSFs in febrile neutropenic patients following standard-dose chemotherapy may benefit some animals considered to be at high risk, but routine use adds unnecessary expense and prolonged administration should be avoided.

Cost Key

$ = < $100	$$$$ = $500–$1000
$$ = $100–$250	$$$$$ = > $1000
$$$ = $250–$500	

CBC = complete blood count; CSF = colony-stimulating factor; G-CSF = granulocyte colony-stimulating factor

Anticipation of Complications

A CBC should be checked before administration of a myelosuppressive agent, and the drug should be administered only if the neutrophil count is above 3000/µl*—especially for animals with any degree of previous neutropenia.

Mild neutropenia (Grade 1): For most patients receiving chemotherapy, the expected nadir of the neutrophil count is between normal and 1500/µl. At this level, the risk for complications is low, but because the time of the true nadir is not known for an individual patient, outpatient prophylactic antibiotics are continued. The dosage of a chemotherapy drug causing mild neutropenia should *not* be changed the next time the drug is administered unless recovery is delayed, requiring the next treatment to be postponed.

Moderate neutropenia (Grade 2): When the neutrophil count is between 1500/µl and 1000/µl following chemotherapy, the risk for complications is still fairly low. However, outpatient prophylactic antibiotics are continued or started in pets that are not receiving them.

The dosage of a drug causing moderate neutropenia does not normally need to be changed the next time the drug is administered. However, veterinarians less experienced in administering chemotherapy may prefer to reduce the dose by 25% for all subsequent doses of *that drug*. If no neutropenia is encountered after the reduced dose, it can be increased by 10% for each administration after which there is no toxicity.

Marked neutropenia (Grade 3): For some animals, the myelosuppressive effects of chemotherapy may be more pronounced; in these pets, the neutrophil count may be between 1000/µl and 500/µl following chemotherapy. At this level, the risk for complications is much higher, although most animals will not develop sepsis as long as they are receiving prophylactic antibiotics. Outpatient prophylactic antibiotics should be continued for animals that are afebrile and showing no clinical signs, or started in pets that are not already receiving them.

A full examination of the patient should be done, but to avoid increasing the risk for sepsis the pet should *not* be hospitalized unless parenteral care is needed. Owners should be instructed to check the temperature at least twice a day, and contact the veterinarian if it is above normal on 2 occasions 30 minutes apart. In addition, any signs of illness (lethargy, vomiting, diarrhea, anorexia) should be reported to the veterinarian promptly and the situation treated as an emergency.

The dosage of a drug causing marked neutropenia should be reduced by 25% for all subsequent doses of that drug and a CBC should be collected at the expected time of nadir; prophylactic antibiotics should be given after the reduced dose. If no neutropenia is encountered after the reduced dose, it can be increased by 10% for each administration after which there is no toxicity.

Severe neutropenia (Grade 4): On rare occasions, the myelosuppressive effects of chemotherapy can be severe. The neutrophil count in pets with severe neutropenia is below 500/µl. At this level, the risk for complications is very high, and some animals will become septic even if they are receiving prophylactic antibiotics.

A full examination should be performed, but again, the pet should not be hospitalized unless it has a fever or parenteral supportive care is needed. Owners should be instructed to check the temperature at least twice a day, contact the veterinarian if it is above normal on 2 occasions 30 minutes apart, and report any signs of illness (lethargy, vomiting, diarrhea, anorexia) promptly.

The dosage of the drug causing severe neutropenia should be reduced by 25% for all subsequent doses of that drug; prophylactic antibiotics should be given after the reduced dose and a CBC collected at the expected time of nadir. If no neutropenia is encountered after the reduced dose, it can be increased by 10% for each administration after which there is no toxicity.

Follow-Up

While many chemotherapeutics have myelosuppressive potential, at the doses used in veterinary medicine most neutropenia caused by chemotherapy is manageable, resulting in minimal impact on the patient's quality of life.

See Aids & Resources, back page, for references, contacts, and appendices.

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A good quality of life is possible for patients receiving chemotherapy, as long as close attention is paid to monitoring for, and preventing, potential toxicity.

* Some experts recommend lower minimal neutrophil counts but we feel that can be risky.