Proceeding of the NAVC
North American Veterinary Conference
Jan. 8-12, 2005, Orlando, Florida

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MANAGING FEBRILE NEUTROPENIA IN THE CHEMOTHERAPY PATIENT

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Chemotherapy is becoming commonplace in veterinary medicine, but because chemotherapy drugs have a particularly narrow margin of safety, adverse effects are often encountered. Neutrophilic complications, including febrile neutropenia, represent the most common adverse effect. Identification and treatment of febrile neutropenia, a potentially fatal complication of chemotherapy, will be discussed in this manuscript. Cats are quite tolerant of chemotherapy and rarely develop febrile neutropenia; therefore most comments herein are directed at dogs undergoing chemotherapy. However similar management principles apply to cats with febrile neutropenia.

Because chemotherapy drugs are designed to disrupt and affect rapidly dividing cells, cancer cells are more likely to be killed than normal host cells, with the exception of bone marrow stem cells. Bone marrow transit time and circulating half life of various cell types predicts their sensitivity to chemotherapy. Neutrophils have a 6 day transit time through the bone marrow and a 4 to 8 hour circulating half-life, platelets have a 3 day transit time and a 4 to 6 day circulating half-life, whereas red blood cells (RBC) have a transit time of 7 days and a circulating half life of 120 days in dogs and 60 to 80 days in cats. Based on these observations, it follows that neutrophil and platelet counts would be most impacted by chemotherapy, and RBC count would be minimally affected. Indeed, neutropenia is the dose-limiting toxicity of most chemotherapy drugs, and chemotherapy-induced anemia is rarely problematic in veterinary medicine. Although tumor cells develop various mechanisms to cope with exposure to cytotoxic drugs, normal bone marrow cells do not and are therefore at risk throughout the duration of chemotherapy, even when the tumor has become refractory.

Neutrophilic complications, such as febrile neutropenia (absolute neutrophil count >1,000/µl with temperature >102.5°F) and severe neutropenia (<1000/µl), often result in morbidity and mortality for cancer patients. Furthermore, these neutrophilic complications result in treatment delays and empirical dose reductions to decrease the risk of future neutrophilic complications. Unfortunately, both delaying treatment and decreasing drug dosages serve to decrease the dose intensity of the chemotherapy protocol. This is important because small decreases in dose intensity can negatively impact the long term survival of the cancer patient without any change in the complete response rate.

The neutrophil nadir (i.e., lowest absolute neutrophil count) typically occurs sometime between days 5 and 7 after chemotherapy administration. However, the neutrophil nadir is not always predictable and can vary significantly between individuals given the same drug and dosage. Likewise, the nadir can be affected by the specific drug given. For example, the neutrophil nadir for cisplatin is biphasic, occurring on days 6 and 15 after administration, whereas the neutrophil nadir after doxorubicin administration may not occur until day 10. Likewise, the severity of the neutrophil nadir may be altered when drugs are given in combination. For example, L-asparaginase has no appreciable effect on the neutrophil count and vincristine does not typically cause significant neutropenia. However, when these two drugs are given simultaneously, as in many chemotherapy protocols for canine lymphoma, there is apparent synergy between vincristine and L-asparaginase often resulting in profound neutropenia.

Most chemotherapy drugs can cause neutropenia, and the effects are largely dose-dependent. As a result some drugs cannot be safely dosed based on body surface area, or the dose is altered for smaller dogs to compensate for shortcomings in the body surface area formula. Moreover, chemotherapy overdoses can result in fatal consequences, in part, due to the resultant severe neutropenia. Therefore, appropriate measures should be in place to double-check the dose calculations and amount of chemotherapy drug administered to each patient to minimize the risk of an accidental overdose.

Neutropenia, in and of itself, does not cause clinical signs. However it does predispose the patient to infection and sepsis, and preexisting occult infections may suddenly become life-threatening. Furthermore, cancer patients may also have compromised defense systems against infection that further increase the risk for morbidity and mortality. Things that may compromise the host's immune system include skin penetrations (venipuncture, central venous lines, intravenous catheters), damaged mucous membranes, depressed ciliary system, urinary bladder catheters, chemotherapy, ionizing radiation therapy, glucocorticoid therapy, underlying malignancy, catabolism, the use of antibiotics that disrupt the normal host flora, decreased humoral and cellular immunity, organ dysfunction, decreased granulocytes, and a depressed monocyte/macrophage system. The relationship between these factors and their consequences is highly complex, and each impacts several immunological factors resulting in an overall increased risk for infection in cancer patients exacerbated by neutropenia.

Frequent hematological monitoring is recommended for all patients undergoing chemotherapy. A complete blood count should be collected immediately before administration of a myelosuppressive chemotherapy drug. In the case of many canine lymphoma protocols, the planned weekly chemotherapy treatments often correspond with the neutrophil nadir of the previous week's drug. If the pre-treatment neutrophil count is <2,500/µl, then the treatment should be delayed, and a CBC should be repeated in 72 hrs, when most patients have a neutrophil count that is >3,500/µl. For drugs that are given every 21 days, a CBC should be checked at the time of the anticipated neutrophil nadir.

If neutropenia is identified, then the risk to the patient can be estimated from its severity. For dogs, neutrophil counts of >1,500/µl are not often associated with fever or clinical illness. However, as the neutrophil count drops <1,000/µl, the risk for septicemia begins to increase exponentially, and dogs with neutrophil counts <200/µl are considered at extreme risk for sepsis. The risk of sepsis in a chemotherapy patient is a function of both the magnitude of the neutropenia and the duration of neutropenia. Although fever is a commonly identified abnormality in dogs with chemotherapy-induced neutropenia, absence of fever does not rule out profound neutropenia or sepsis. The animal may simply have too few granulocytes to mount a successful febrile response. Neutropenia is problematic for chemotherapy patients because the nadir can coincide with the peak effects on the gastrointestinal mucosa, allowing easier translocation of bacteria.
Animals that have chemotherapy-induced neutropenia should be managed aggressively on the basis of the absolute neutrophil count and in view of their clinical presentation. For animals that are moderately neutropenic (1,500 – 1,000/µl), with normal body temperature and no clinical signs, close monitoring at home by the owner is appropriate, which might include taking the rectal temperature of dogs. Beginning prophylactic antibiotic therapy is advisable, and the choice of drug should have minimal impact on the normal gastrointestinal flora.Trimethoprim/sulfa and quinolone antibiotics are often used in this situation. For the moderately neutropenic dog with a fever (> 102.5 F) or clinical signs, such as lethargy, depression, inappetence, vomiting, or diarrhea, aggressive therapy should be started. The animal should be hospitalized, monitored closely (temperature, pulse, respiration, blood glucose, etc.), and started on intravenous fluids and antibiotics. Likewise, severely neutropenic patients should be hospitalized immediately, regardless of the presence of clinical signs.

When the neutropenic chemotherapy patient is admitted to the hospital, a complete blood count, serum biochemistry profile, and urinalysis should be done immediately. Before antibiotic therapy is begun, the necessary samples for aerobic and anaerobic blood and urine cultures should be collected. Although blood cultures are often low-yield, when positive, they can accurately guide antimicrobial therapy. Once these samples are collected intravenous antibiotic therapy can be started along with fluid therapy. Until culture results are available, or in the absence of a positive culture, antibiotic therapy for the neutropenic chemotherapy patient is largely empirical. Gram positive bacteria often cause problems for neutropenic patients, especially those that have received prophylactic quinolone antibiotics. In humans undergoing chemotherapy, prophylactic quinolone antibiotic therapy has been shown to increase the likelihood of colonization of the oral cavity with resistant Streptococcus species. Infections with Staphylococcus species may come from venipuncture sites, intravenous catheters, or other breaks in the skin. Gram negative bacteria may also be problematic if they translocate from the gastrointestinal tract. Therefore, antibiotic therapy should be broad spectrum and designed to deal with both Gram positive and Gram negative bacteria.

Examples of common antibiotic choices for treating febrile neutropenia in veterinary patients include the combination of enrofloxacin and ampicillin, single agent ticarcillin/clavulanate (Timentin®), or the combination of ampicillin and gentamicin. Perhaps the most important consideration in choosing antibiotic therapy is the sensitivity of the resident pathogenic bacteria in the treatment facility. Hospitals offering chemotherapy should routinely monitor the sensitivity patterns of the nosocomial infections that occur to identify the emergence of antibiotic resistant species. Treating febrile neutropenic chemotherapy patients with antibiotics lethal to the local problematic bacteria will decrease the morbidity and mortality of this patient population. If the patient does not begin to improve within 24 hours of instituting antibiotic therapy and is persistently febrile, then the antibiotic regimen should be reevaluated and possibly modified to include drugs like metronidazole or a 3rd generation cephalosporin. Diagnostic imaging might also be warranted to search for specific foci of infection.

Other problems that may occur in neutropenic chemotherapy patients include electrolyte abnormalities, hypoglycemia, signs of shock, and disseminated intravascular coagulation (DIC). Electrolyte abnormalities and hypoglycemia can be managed through appropriate fluid therapy. Shock and DIC should be treated aggressively in a septic patient. Regular assessment of blood glucose concentration, PCV, total protein, prothrombin time (PTT), partial thromboplastin time (PTT), fibrinogen, and fibrinogen degradation products (FDP) in the critically ill neutropenic chemotherapy patient is warranted to quickly identify and treat potentially life-threatening complications of sepsis. A CBC should be repeated approximately 24 hours after initiation of therapy to determine whether the neutrophil count is worsening, improving, or static. The rate of bone marrow recovery depends on several factors, including the magnitude of neutropenia, the time elapsed since the offending chemotherapy dose, and the specific drug given.

Intravenous fluid therapy and intravenous antibiotics should be continued until clinical signs resolve and the dog is eating and drinking and can tolerate oral antibiotic therapy. In most cases of febrile neutropenia, the dogs recover quickly and uneventfully, but dogs with sepsis may have a considerably longer recovery. Deciding when to discharge the patient from the hospital can be difficult, as there are clearly risks associated with prolonged hospitalization of an immunocompromised patient. However if the clinical signs have resolved, the patient is eating and drinking, and the neutrophil count is beginning to improve, then it may be safer for the dog to be at home even if the dog is still moderately neutropenic.

The use of growth factors such as filgrastim (Neupogen®), a recombinant human granulocyte colony-stimulating factor (G-CSF), for managing febrile neutropenia in veterinary patients remains controversial. In cases of established neutropenia, G-CSF is probably of limited value. However, it may be useful in increasing the neutrophil count before the chemotherapy-induced neutrophil nadir to prevent neutropenia. But without controlled clinical trials to document its efficacy in improving the outcome of chemotherapy or decreasing the incidence of febrile neutropenia in dogs, the expense of the drug may not be easily justified.

Simple management strategies can often prevent or minimize the severity of febrile neutropenia in canine chemotherapy patients. First is frequent hematological monitoring. A pre-treatment CBC prevents the administration of myelosuppressive drugs to a dog with neutropenia and a CBC at the predicted nadir for the drug allows an assessment of the bone marrow effects, especially when clinical signs are not present. Another effective management tool is monitoring the body temperature. Most dog owners can be taught to take a rectal temperature; however, this method of monitoring is not typically recommended for cats given the relative infrequency of neutrophilic complications in cat combined with their general disposition towards repeated encounters with the rectal thermometer. By taking their dog’s rectal temperature once each day while the dog is at rest, the owner learns the normal temperature of their pet. Moreover, they can detect the beginnings of a fever before clinical signs are evident allowing for timely antibiotic therapy. By starting prophylactic oral antibiotic therapy when the body temperature is ≥ 102.5 F, the potential for life-threatening sepsis is greatly reduced. This strategy not only improves the patient’s quality of life but also saves the owner a significant amount of money by not having to treat a critically ill dog. Because chemotherapy is a costly affair, some owners elect euthanasia if faced with the added expenses associated with hospitalization of a septic pet. Therefore owners should be
counseled about the possibility of neutrophilic complications at the onset of chemotherapy and every effort made to minimize the risks.

Recognizing that febrile neutropenia is a cause of significant morbidity and mortality in veterinary cancer patients has allowed the development of successful prevention and treatment strategies. These improvements in the care of chemotherapy patients may represent the most significant advance in the medical management of veterinary cancer patients in the past 3 decades. With quick identification of neutrophilic complications and appropriate aggressive therapy, morbidity and mortality can be decreased.

SUGGESTED READING