A number of established immunosuppressive agents have been used in small animal medicine for many decades. Some have justifiably fallen out of favor whereas, for others, new and promising uses have been described in the recent veterinary literature. This lecture will discuss some ‘old favorites’: cyclophosphamide, chlorambucil, azathioprine, danazol and vincristine.

**Cyclophosphamide**

Cyclophosphamide, a cell-cycle nonspecific nitrogen mustard derivative alkylating agent, was one of the first major chemotherapeutic agents approved by the FDA over 50 years ago, and has since become very well-established in human medicine as both an antineoplastic drug and as an immunosuppressive agent. Within a few years of FDA approval in the late 1950s, the use of cyclophosphamide for the prevention of transplant rejection in experimental models and for the treatment of both neoplasia and immune-mediated diseases was described in both dogs and cats. Cyclophosphamide has persisted to this day as one of the core drugs used in many small animal cancer chemotherapeutic protocols. In contrast, after many years as one of the most commonly immunosuppressive drugs utilized to treat immune-mediated diseases in cats and dogs, the use of cyclophosphamide as an immunosuppressive agent in small animal patients has in the past two decades essentially faded away. The reasons for the steadily diminishing popularity of cyclophosphamide as an immunosuppressive agent are myriad, and include a high incidence of unacceptable side effects, the development of other immunosuppressive agents that are generally safer and more convenient to administer, and the publication of a number of papers a decade or so ago that suggested that cyclophosphamide was associated with poor outcomes when used to treat conditions such as immune-mediated hemolytic anemia.

Cyclophosphamide is a produg that is metabolized by the hepatic cytochrome P450 enzyme system to eventually form active metabolites such as 4-hydroxycyclophosphamide, 4-hydroperoxycyclophosphamide, and aldophosphamide. These metabolites can enter cell cytoplasm, where they are ultimately metabolized to phosphoramide mustard and acrolein. Phosphoramide mustard is an alkylating agent that replaces a hydrogen atom with an alkyl group on the guanine base of DNA, which interferes with nuclear DNA replication and cytoplasmic RNA transcription by forming crosslinks both within and between nucleotide strands. Cyclophosphamide has long been reported to be a potent immunosuppressive that inhibits humoral and cell-mediated immunity, including inhibition of primary and secondary immune responses, reduction of antigen trapping in lymph nodes, and inhibition of local inflammatory responses, although in a number of experimental studies in dogs, cyclophosphamide often appears to be relatively mildly immunosuppressive compared to other drugs.

Cyclophosphamide shares the toxicity profile of most alkylating agents, with common side effects including gastrointestinal signs, myelosuppression, and hair loss. Gastrointestinal signs
are relatively common, and include nausea, anorexia, vomiting and diarrhea. Dose reduction and antiemetic agents are often enough to control gastrointestinal signs, but occasionally persistent gastrointestinal side effects will prevent ongoing use of the drug, especially in cats.

Myelosuppression appears to be dose dependent, and is associated with both the use of high drug doses and the use of lower doses over a sustained period of time. Moderate to severe neutropenia is the most potentially life-threatening feature of cyclophosphamide myelosuppression, but moderate thrombocytopenia and mild anemia may also occur. Neutropenia is typically reversible with drug dose reduction or discontinuance, but can occasionally persist for weeks or even months, particularly after chronic cyclophosphamide therapy. Recombinant granulocyte colony-stimulating factor can be used to hasten recovery in dogs with severe cyclophosphamide-induced neutropenia. Alopecia is most common in susceptible breeds such as poodles and old English sheepdogs. Interestingly, cyclophosphamide has been used in the past to ‘chemically shear’ sheep.

A major side effect of cyclophosphamide that is (to a large extent) unique to this drug is the development sterile hemorrhagic cystitis. Cystitis is mediated by urinary excretion of the cyclophosphamide metabolite acrolein. Cystitis is often severe and debilitating to the patient, and will not resolve until the drug is discontinued. Unfortunately, distressing signs of cystitis can sometimes persist for days or even weeks after drug discontinuation. Cystitis is more likely to develop after long-term therapy with cyclophosphamide, which can present a particular problem for patients with immune-mediated diseases because such diseases are often persistent, and tend to relapse if immunosuppressive therapy is discontinued prematurely. The incidence of cystitis can be reduced significantly by the concurrent administration of furosemide or sodium 2-mercaptoethane sulfonate (mesna), a sulfhydryl donor that binds acrolein, by ensuring ready access to water, and by taking canine patients for regular walks. The chronic local bladder inflammatory effects of cyclophosphamide have also been reported to predispose to the development of irreversible bladder wall fibrosis and transitional cell carcinoma.

Over the years, a number of immune-mediated and inflammatory diseases in dogs and cats have been treated with cyclophosphamide, including immune-mediated hemolytic anemia (IMHA), immune-mediated thrombocytopenia, megakaryocyte hypoplasia; pure red cell aplasia, systemic lupus erythematosus, immune-mediated polyarthritis, inflammatory bowel disease, glomerulonephritis, noninfectious inflammatory meningoencephalitis, immune-mediated vasculitis and pemphigus. For many years, cyclophosphamide was considered a ‘big gun’ to be used in dogs with severe or life-threatening IMHA. However, in the late 1990s and early 2000s, a number of case studies were published that suggested that, at best, cyclophosphamide was not better than glucocorticoids alone for the treatment of IMHA and, at worst, associated with a higher than expected mortality rate. Given the known limitations of retrospective studies, including the associated potential for ‘case selection bias’ (that is, the dogs with the most severe IMHA may have been given cyclophosphamide because it was the drug perceived to be most potent), it is hard to know with any real certainty whether cyclophosphamide actually worsens prognosis in dogs with IMHA. Nevertheless, there is no doubt that, since publication of these papers, the use of cyclophosphamide to treat conditions such as canine IMHA has markedly decreased.

Compared to many immunosuppressive agents, cyclophosphamide is relatively cheap, with a generic 25 mg tablet costing under $2, and a 50 mg tablet costing under $4. One of the major
problems associated with using cyclophosphamide as an immunosuppressive agent is that it is difficult to dose accurately, and even more difficult to taper, especially in smaller patients. Cyclophosphamide is available as 25 or 50 mg tablets that composed of an active inner tablet surrounded by an inert outer flecked tablet. Because of uneven distribution of the drug through the tablet, cyclophosphamide tablets cannot be split or crushed without a risk of major dosing inaccuracies. Without drug compounding, cyclophosphamide doses must therefore be in multiples of 25 or 50. Published immunosuppressive doses for cyclophosphamide in dogs include 50 mg/m² or 1.5 to 2.5 mg/kg every second day or daily on a ‘4 days on, 3 days off’ weekly protocol. In cats and small dogs, similar total weekly doses can be used, but ‘pulsed’ at infrequent dosing intervals that ensure that the total weekly dose is equivalent to seven times the calculated daily dose. Since myelosuppression can occur at any time during chronic cyclophosphamide therapy, complete blood counts must be performed regularly throughout the course of drug treatment. Cyclophosphamide is available in an intravenous form as well as an oral form, and a recent study in dogs confirmed that equivalent oral and intravenous doses of cyclophosphamide achieved comparable blood levels of the active metabolite 4-hydroxycyclophosphamide. Intravenous cyclophosphamide may therefore be a viable treatment option in vomiting animals that are unable to tolerate oral immunosuppressive agents.

**Chlorambucil**

Chlorambucil is a nitrogen mustard derivative cell-cycle nonspecific alkylating agent that has, for many decades, been used in both human and veterinary medicine predominantly as an antineoplastic agent for the treatment of cancers such as lymphoid leukemia, lymphoma, mast cell tumors, multiple myeloma and polycythemia vera. Antineoplastic cytotoxicity is derived from inappropriate cross-linkage of cellular DNA and RNA by insertion of alkyl radicals on the purine base, guanine. Chlorambucil also has immunosuppressive properties, and has occasionally been used in human medicine to treat immune-mediated and inflammatory conditions such as glomerulonephritis. More than 30 years ago, some veterinary clinicians began suggesting the use of chlorambucil as an immunosuppressive agent for our small animal patients. Since then, the use of chlorambucil for the treatment of a number of feline inflammatory skin conditions, such as pemphigus and eosinophilic granuloma complex, and for treatment of diseases such as immune-mediated thrombocytopenia and refractory inflammatory bowel disease, has become very well established, primarily because of a paucity of viable alternative medications that could be accurately dosed with safety in cats. The use of chlorambucil as immunosuppressive agent in dogs has been slower to evolve, but its use has been described for the treatment of pemphigus, glomerulonephritis and, most recently, inflammatory bowel disease. It is somewhat surprising that chlorambucil has not attained more common usage as an immunosuppressive agent in dogs, since it appears to have much the same mechanism of action as cyclophosphamide with significantly less onerous side effects (specifically, chlorambucil does not cause sterile cystitis), and comes in a more convenient tablet size.

Chlorambucil is metabolized predominantly in the liver, primarily to the active metabolite phenylacetic acid mustard. Compared to other alkylating agents, chlorambucil is relatively well tolerated, especially at immunosuppressive doses, but does occasionally cause gastrointestinal side effects such as vomiting and diarrhea, and/or myelosuppression with neutropenia, thrombocytopenia and non-regenerative anemia (anemia is usually mild). Alopecia and poor hair growth are sometimes reported in susceptible dog breeds, such as poodles. Neurologic side
effects are reported with chronic chlorambucil use in people, and chlorambucil-associated neurologic signs (including myoclonus, twitches and seizures) have been reported in cats.

Chlorambucil is available as a coated 2 mg tablet that cannot feasibly be divided, and dosing recommendations in smaller patients are therefore typically provided in multiples of two, and/or ‘pulsed’ at infrequent dosing intervals (given at an interval that ensures the overall weekly dose is equivalent to seven times the calculated daily dose) in order to avoid overdose. For immunosuppressive therapy, chlorambucil is almost always given in combination with an oral glucocorticoid. In dogs, recommended starting oral immunosuppressive chlorambucil doses (with a glucocorticoid) range from 0.1 to 0.2 mg/kg (or, alternatively, 4 to 6 mg/m²) every one to two days, with dosing individualized based on patient size and disease severity. In cats (and small dogs) with inflammatory or immune-mediated disease, a starting oral chlorambucil dose of 2 mg every second day (with a glucocorticoid), tapered to every 3rd or 4th day, is my preferred dosing regime, although a number of other tapered dosing protocols are also available. Lower daily doses of chlorambucil, comparable to dog dosing regimes, can also be used in cats if the drug is compounded, but the effects of compounding on drug efficacy have not been established. Complete blood counts must be monitored regularly (weekly at first) and, since myelosuppression tends to be dose-dependent rather than idiosyncratic, doses can be tapered ‘to effect’ rather than discontinued completely. Myelosuppression, provided it is detected promptly, is typically reversible.

Compared to many other immunosuppressive agents, chlorambucil has until recently been moderately priced. Unfortunately, the patent on the only available chlorambucil product, Leukeran®, recently expired, leading to a change in ownership of the company responsible for distributing the drug, and the US price of chlorambucil has doubled as a result, to over $10 for a 2 mg tablet. There are currently no other US generic alternatives, apart from compounded products.

**Azathioprine**

Azathioprine has been used as an immunosuppressive agent in dogs for over 50 years. The drug was initially primarily used in studies that utilized dogs as a model for investigations of organ transplantation and the effects of immunosuppression on various body systems. Within a few years, azathioprine was also being used to treat naturally occurring diseases in dogs. Despite almost half a century of cumulative clinical and research experience on the use of azathioprine in dogs, however, there have been remarkably few studies that actually elucidate the precise effects that azathioprine has on the canine immune system. Most of our understanding of the mechanism of action of azathioprine in dogs is extrapolated from work in other species.

Azathioprine is a prodrug for the active metabolite 6-mercaptopurine, and the primary mechanism of action was long believed to be inhibition of the synthesis of the purines adenine and guanine by blockage of enzymes such as amidophosphoribosyltransferase, with resultant production of nonfunctional nucleic acid strands. Disruption of purine synthesis inhibits DNA and RNA synthesis, thereby inhibiting the proliferation of fast-growing cells such as lymphocytes. In the past few decades, however, multiple other mechanisms of action mediated by various azathioprine metabolites have been proposed, including blockage of T cell activation and stimulation of T cell apoptosis. Azathioprine has long been reported to be more effective against T cell function than B cell function, although strong evidence supporting this is lacking.
One of the key enzymes involved in azathioprine metabolism and inactivation is thiopurine methyltransferase (TPMT). Individual human patients (about one in 300 people) inherit a marked deficiency in the TPMT enzyme that renders them highly susceptible to azathioprine toxicity, particularly life-threatening bone marrow suppression. Interestingly, cats have also been shown to have a marked deficiency in TPMT enzyme activity, which may explain why azathioprine causes marked myelosuppression in cats at standard canine doses. Although the use of azathioprine at a very reduced dose rates has previously been published in cats, given the narrow margin for safety it is probably wisest to recommend that azathioprine never be used in cats at any dose, especially considering the availability of other immunosuppressive agents that appear to be much safer in cats, such as chlorambucil and cyclosporine. Although TPMT expression in dogs is widely variable, severe deficiencies in enzyme activity of the magnitude seen in cats and some people have not been commonly reported, and TPMT deficiency does not appear to be associated with the severe drug toxicities sometimes seen in dogs.

The standard azathioprine starting dose in dogs is 2 mg/kg orally once daily. This dose is usually well-tolerated and, although gastrointestinal side effects such as nausea, anorexia, vomiting and diarrhea are occasionally reported, they are typically mild and self-limiting. Although, in dogs, marked myelosuppression is uncommon, chronic azathioprine usage almost invariably causes a mild to moderate poorly regenerative anemia. Since anemia is an expected outcome in dogs receiving azathioprine, and is typically very well tolerated (that is, sub-clinical), mild to moderate anemia alone should not be mistaken as evidence of either drug overdose or treatment failure. Uncommonly, azathioprine can also cause profound myelosuppression or severe hepatotoxicity in dogs. Marked myelosuppression and hepatotoxicity appear to be idiosyncratic non-dose-dependent drug reactions (Type B reactions), and are typically reversible if the problem is recognized early enough and azathioprine is discontinued. Complete blood counts and serum biochemistry panels (especially ALT) should therefore be monitored regularly during initial azathioprine therapy. Several individual case reports have also reported pancreatitis in dogs receiving azathioprine, but cause and effect has not been established.

Azathioprine has, over the years, become well-established as an ‘add on’ immunosuppressive agent to be considered for the treatment of many different immune-mediated and inflammatory conditions when glucocorticoids alone are ineffective or poorly tolerated, including immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, inflammatory bowel disease, chronic hepatitis, glomerulonephritis, immune-mediated polyarthritis, myasthenia gravis, non-infectious meningoencephalitis, immune-mediated skin diseases, and anal furunculosis. Despite decades of azathioprine usage, evidence supporting immunosuppressive efficacy for many of these common diseases is remarkably limited. Interestingly, because (despite a relative paucity of evidence) azathioprine has commonly been recommended as the standard immunosuppressive drug of choice for many conditions, the efficacy of newer drugs for the treatment of these conditions is sometimes compared to a parallel group receiving azathioprine. One perceived ‘limitation’ of azathioprine compared to other immunosuppressive agents, that it can take many weeks or even months to exert its effects, is based on limited and dated data derived predominantly in humans. In my experience, azathioprine in a clinical setting exerts its immunosuppressive effects in dogs about as rapidly as most other comparable agents.

Compared to most other immunosuppressive agents, azathioprine is relatively inexpensive, which is an important consideration with long-term immunosuppressive therapy, especially in
large dogs. While the proprietary product (Imuran® or Azasan®) typically still costs over $5 per 50 mg tablet, the generic equivalent can be obtained for less than $1 a tablet. The smallest tablet size is 50 mg (although tablet scoring permits a 25 mg dose), which can present dosing problems in small (under 20 lb) dogs.

**Danazol**

Danazol, a synthetic androgen with weak (‘impeded’) androgenic effects, has in the past been suggested for the treatment of canine immune-mediated hemolytic anemia and immune-mediated thrombocytopenia, in combination with glucocorticoids, in order to reduce the dose of steroid that is needed. Danazol is derived from the synthetic steroid ethisterone, a modified progestogen. Danazol’s most important mechanism of action is probably to reduce macrophage Fc receptor/antibody binding affinity. Danazol also competes with glucocorticoids for combination with steroid-binding globulin, consequently increasing the availability of active unbound glucocorticoid. Concurrent danazol therefore enables significant glucocorticoid dose reduction. Danazol may also reduce the degree of binding of antibody and complement to the red blood cell or platelet surface. Side effects are uncommon, and include hepatotoxicity and masculinization of female dogs. However, although some dogs with refractory IMHA and IMT have been reported to benefit from danazol, the drug fell out of favor a few decades ago, probably because it was very expensive at the time, and response to therapy was sluggish and highly unpredictable.

Reported oral danazol doses in dogs with IMHA or IMT, in combination with glucocorticoids, range from 5 to 15 mg/kg daily, either given as a single dose or 2-3 divided doses. Danazol comes in 50 mg, 100 mg, and 200 mg capsules. Danazol currently costs a little less than $2 for a 50 mg capsule.

**Vincristine**

The vinca alkaloids are biologically-active dimeric alkaloids derived from the Madagascar (or rosy) periwinkle plant, Catharanthus roseus. Vincristine, a naturally-occurring vinca alkaloid, were originally characterized phytochemically more than fifty years ago. The diverse biological effects of vincristine have traditionally been attributed to drug-induced disruption of various intracellular microtubules. Microtubules are elongated, tubular cytoplasmic organelles involved in a broad spectrum of cellular processes including chromosomal migration, conduction of cellular secretions, ciliary and flagellar motility, and maintenance of cell shape. Microtubules are composed predominantly of complex helical polymers of the structural protein tubulin. Vincristine binds directly to tubulin, causing both inhibition of microtubule synthesis and disruption of intact microtubules. Microtubular structures susceptible to the effects of vinca-tubulin binding include the mitotic spindle in dividing cells, the neurotubules in neurons, and the cytoskeletal microtubules in platelets. Vincristine may also exert biological effects that are independent of disruption of intracellular microtubules, such as inhibition of RNA, DNA and protein synthesis, and modification of prostaglandin production.

Vincristine is a cell-cycle-specific cytotoxic agent. Vincristine disrupts microtubules within the mitotic spindle of dividing cells, thereby arresting chromosomal separation in metaphase. Vincristine at standard therapeutic doses is minimally myelotoxic, and is therefore commonly used in combination with more myelosuppressive chemotherapeutic agents. Vincristine is
frequently used in veterinary cancer chemotherapy, both as a single agent for the treatment of canine transmissible venereal tumors, and as a component of combination protocols for the treatment of acute leukemia, lymphoreticular neoplasms, mast cell tumors, and various carcinomas and sarcomas.

Vincristine is usually administered intravenously as a sulfate salt, which is chemically more stable than its corresponding free base. Inadvertent subcutaneous or intramuscular administration causes severe local tissue irritation and necrosis. Oral absorption of vincristine is poor. Plasma disappearance of vincristine following intravenous administration is markedly biphasic, with a short initial half-life and a prolonged terminal half-life. The short initial clearance phase reflects extensive extravascular drug redistribution due to a combination of both avid binding to intracellular tubulin and rapid biliary excretion. The prolonged terminal clearance phase is due to the gradual release of vincristine bound to circulating plasma proteins and intracellular tubulin. Platelets demonstrate a remarkable ability to concentrate vincristine from plasma, and are therefore the principal circulating cellular carriers of the drug.

The degree of immunosuppression induced by vincristine at intravenous therapeutic doses is minimal compared to that induced by glucocorticoids, cyclophosphamide or azathioprine, and vincristine therefore is not used as an immunosuppressive agent for the treatment of most immune-mediated or inflammatory diseases in dogs and cats. The one exception is immune-mediated thrombocytopenia (IMT), where vincristine has become a mainstay of treatment.

During early clinical trials in human cancer patients, it was observed that the administration of vincristine was frequently associated significant but transient increases in circulating platelet numbers. A similar phenomenon has since been reported in dogs, both in research animals and in cancer patients. This effect appears to be due to increased megakaryocytosis and thrombopoiesis, although the precise mechanisms of vincristine-associated thrombocytosis are still uncertain. Circulating platelet life-span does not appear to be significantly affected by standard low doses of vincristine in healthy animals.

The serendipitous discovery that vincristine induced thrombocytosis in human cancer patients with normal pre-treatment platelet numbers prompted conjecture that a similar outcome could be obtained in thrombocytopenic patients. Following publication of several anecdotal reports describing prompt, marked increases in circulating platelet numbers after administration of vincristine to people with IMT, vincristine gained favor with some hematologists as the treatment of choice for chronic refractory IMT. Vincristine frequently induces partial or complete remission of thrombocytopenia within one week of commencing therapy, although such remissions are typically transient. Only a relatively small proportion of human chronic refractory IMT patients achieve complete sustained remission with vincristine therapy.

Rapid drug clearance from plasma reduces the therapeutic efficacy of a standard intravenous bolus of vincristine. Several alternate methods of vincristine administration have therefore been used in human IMT patients in order to sustain therapeutic plasma concentrations. Constant intravenous vincristine infusion (over six to eight hours) effectively maintains therapeutic plasma concentrations throughout the period of administration. Alternatively, the ability of platelets to concentrate vinca alkaloids from plasma has been utilized to enhance therapeutic efficacy via transfusion of vincristine-loaded platelets. Incubation of donor platelets in high concentrations of vincristine (vinca loading) prior to transfusion maximizes intracellular vinca-
tubulin binding. Following transfusion, circulating vinca-loaded donor platelets gradually release vincristine into the recipient's plasma, thereby sustaining therapeutic plasma drug concentrations. Both constant rate infusion with vincristine and transfusion with vinca-loaded platelets induce sustained remissions in some human chronic IMT patients previously refractory to single intravenous boluses of the drug.

Vincristine, typically in combination with prednisone, has been reported to similarly facilitate remission of thrombocytopenia in many canine patients with IMT. Original case reports demonstrating an apparent rapid response to vincristine in dogs with IMT have been supported, decades later, by evidence obtained from prospective studies. Circulating platelet numbers increase markedly within three to five days of vincristine administration in responsive dogs, and the addition of vincristine to standard immunosuppressive therapy in dogs with IMT appears to shorten hospitalization time by several days. Most authors currently recommend an intravenous vincristine bolus dose of 0.02 mg/kg for the treatment of canine IMT. Vincristine boluses may subsequently be repeated weekly if thrombocytopenia recurs. Apparent rapid clinical response to vincristine-loaded platelets has been reported in one dog with refractory IMT. Vincristine has been used in cats with IMT, although evidence of clinical efficacy is lacking. One significant advantage of vincristine compared to other therapeutic options for IMT (such as human intravenous globulin) is that vincristine is inexpensive (a 1 ml vial of 1mg/ml vincristine sulfate costs around $20).

The pathogenesis of vincristine-induced remission of thrombocytopenia in IMT patients is uncertain. Clinicians initially assumed that remissions were due to increased megakaryocyte production and release of platelets, the principal mechanism assumed to underlie the vinca-induced thrombocytosis seen in healthy animals and cancer patients. However, since IMT patients typically already have high levels of circulating thrombopoietic factors and maximal thrombopoiesis, platelet precursors may be refractory to further stimulation by vincristine. Furthermore, studies in people suggest that the main therapeutic effect of vincristine in IMT patients is not increased thrombopoiesis. Post-treatment average platelet life-spans are significantly prolonged in human IMT patients that respond to vincristine, suggesting that remission is due to reduced platelet destruction rather than increased platelet production. Since platelets are the major circulating cellular carriers of vincristine, researchers have speculated that antibody-coated platelets selectively deliver vincristine to those phagocytes within the mononuclear phagocytic system that are actively involved in platelet destruction. This proposed mechanism explains why, despite being an ineffective immunosuppressive agent for the treatment of most conditions, vincristine can still be very effective for the treatment of IMT.

During electron microscopic studies of platelet ultrastructure, it was discovered that prolonged incubation of platelets in vincristine solutions caused marked disruption of cytoskeletal microtubules. Laboratory investigations have since demonstrated that as well as disrupting platelet structure, exposure to high concentrations of vincristine also significantly impairs platelet function. Based on the in vitro evidence that exposure to vincristine impairs platelet function, hematologists expressed concern that using the drug in patients with IMT could similarly induce platelet dysfunction. Subsequent studies revealed that vincristine affected platelet function (aggregation) in dogs with lymphoma, but not in healthy dogs. Since several recent prospective studies showed no significant increase in bleeding in IMT dogs receiving
vincristine, the effect of vincristine on platelet function, if it occurs, does not appear to be severe enough to be clinically significant.

Neurotoxicity, although uncommon, is the most frequent significant side-effect associated with therapeutic doses of vincristine in dogs and cats. Reversible vincristine-induced neurotoxicity in the dog has been reported with chronic cancer chemotherapy, but is not likely to be an issue with the single doses used to treat IMT. Other side-effects such as gastrointestinal disorders (including megaesophagus and gastric hypomotility) and alopecia, occur less frequently and are typically mild and temporary. Vincristine at doses used for IMT typically causes minimal myelosuppression in dogs, although dogs with the ABCB1-1Δ (MDR1) gene mutation and some Border Collies have been reported to be more susceptible than other dog breeds to myelosuppression at antineoplastic vincristine doses. In affected Border Collies, this effect appears to sometimes be independent of the MDR1 gene mutation reported in this breed. Temporary erythrodysplasia of erythroid precursors in the bone marrow and peripheral blood smears, featuring bizarre mitotic figures, abnormal nuclear configurations, and Howell-Jolly bodies, can be observed after administration of vincristine in dogs, but is of little clinical significance. An unusual transient pulmonary toxicity has been reported in a cat receiving chemotherapeutic doses of vincristine. Vincristine has no known mutagenic or carcinogenic potential.

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Given the high price of many human immunosuppressive agents, and also given the dosing difficulties associated with giving human tablet and capsule sizes to our smaller patients, veterinarians are often tempted to instead use compounded equivalents of these drugs. Compounded versions of many of these drugs can be found at on-line pharmacies that cater to the veterinary market at attractive prices and convenient dosing sizes. However, the bioavailability and clinical efficacy of most of these products in our patients is not established and, with the few drugs where the compounded version has been evaluated (cyclosporine, for example), drug bioavailability was markedly variable and often led to subtherapeutic blood concentrations. Using these products in our patients, especially in those animals with life-threatening disease, therefore represents a major gamble.

In animals that are difficult to give pills to, it is tempting to use a liquid compounded formulation. However, many of the common immunosuppressive agents are potentially mutagenic, carcinogenic and teratogenic. In fractious animals that end up with more medication on their whiskers and fur than in their mouth, given liquid suspensions has the potential to significantly increase the level of owner exposure to these potentially dangerous drugs.