Chlorambucil

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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, protein-losing enteropathy associated with inflammatory bowel disease, with a promisingly high success rate. 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, and in one dog in a recent case report. Recently, acquired Fanconi syndrome has also been reported in cats on chlorambucil.

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/m^2) 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 compounded product, as with cyclophosphamide, has been shown to be associated with significant dosage variability when obtained from veterinary compounding pharmacies. 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. Anecdotally, myelosuppression can sometimes be delayed, especially in cats, and first appear up to one year into chronic low-dose chlorambucil therapy, and can either affect all cell lines, or particularly impact platelet counts.

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 quadrupled as a result, to over $25 for a 2 mg tablet. There are currently no other US generic alternatives, apart from compounded products. The efficacy of compounded chlorambucil in dogs and cats has not been established, although anecdotally veterinarians have reported success when switching from the proprietary to the compounded product.