

Treatment of Canine Lymphoma as a Model for Humans

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Canine lymphoma demonstrates histopathologic and biologic features that are similar to non-Hodgkin's lymphoma (NHL) in humans [1]. Canine non-Hodgkin lymphoma (cNHL) is the most common malignancy in dogs, accounting for up to 24% of all reported neoplasms and 83% of hemopoietic neoplasms [2].

The aetiology of NHL in dogs and human is reported to be multifactorial, with possible contributing agents including viral infections, genetic predisposition, immunosuppression and environmental factors [3-6].

For the diagnosis of multicentric lymphoma in dogs, a fine needle biopsy of a peripheral lymph node and a cytological smear are often requested. In addition, haematological and biochemical profiles, a bone marrow smear, immunophenotyping (B or T), RX and ultrasonography are required for both staging and prognosis. Lymphoma can be subdivided into high and low-grade malignancy and as T- or B-immunophenotype. The most common presentation in dogs is high-grade malignant B cell lymphoma with generalized lymphadenopathy (multicentric). In this animal species, high grade T cell lymphomas are the most uncommon forms, these have a worse prognosis compared to the B immunophenotype [7,8].

In human beings diagnosis, staging and prognosis of NHL relies on information obtained from a biopsy specimen, blood chemistries and complete blood count, bilateral iliac crest marrow biopsies, immunohistochemistry, cytogenetics, ultrasonography and magnetic resonance imaging [9].

Many types of treatment have been proposed for cNHL but the most commonly used is chemotherapy. Single agent protocols were initially used (i.e. doxorubicin, cyclophosphamide), but nowadays multiple agent chemotherapy is the most common approach to NHL and cNHL [10]. In both human and canine patients, the multiple agent chemotherapy protocol based on corticosteroids, vincristine, cyclophosphamide and doxorubicin is still most widely used: it has been termed "CHOP", an acronym incorporating names of the active ingredients.

The treatment of dogs affected by cNHL is divided into several phases: induction of remission, intensification, maintenance and reinduction of remission or "rescue". The basic induction protocol utilises CHOP [11]. For intensification in dogs with partial remission, use of the L-asparaginase enzyme is suggested [11]. During the maintenance phase, a protocol based on chlorambucil, methotrexate and prednisone is scheduled. The modified "Madison-Wisconsin Protocol" is widely used in dogs and consists of a weekly administration of alternate drugs (L-asparaginase, vincristine, cyclophosphamide, prednisone, and doxorubicin) with or without maintenance phase after 6 weeks [12].

In human patients with diffuse large B-cell lymphoma (the most common type of aggressive NHL); rituximab is a viable treatment option in patients with relapsed or refractory indolent NHL. It is also used as a standard first-line treatment option when combined with CHOP or other multiple agent chemotherapies [13,14].

Currently, response to chemotherapy in multicentric B-cell cNHL is about 80%. Unfortunately, it is not curative but induces remission

with a good quality of life for dogs. The median survival in B-cell cNHL in treated dogs is about 12 months. Twenty % of these subjects survive for two years [2,12]. In contrast, CHOP treatment of aggressive B-cell lineage lymphomas produced a complete response rate of 40 to 55% with 30-45% of long term survivors in humans (up to 5 years) [15].

The CHOP and other protocols are generally unsuccessful for the treatment of T-cell cNHL and some authors included CCNU (Lomustine) in the management of these patients [16]. In treated dogs affected by high grade malignant T-cell cNHL, the median survival time was about 6-12 months [12].

Nowadays, the ultimate therapy for both humans and dogs is vaccine treatment. In recent times the genetic vaccine Targeting Dog Telomerase (dTERT), based on Ad/DNA-EP technology (Adenovirus and DNA electroporation), has been found to induce strong immune responses and increased overall survival of dogs affected by B-cell lymphoma in comparison with controls when combined with a COP (corticosteroids, vincristine, and cyclophosphamide) chemotherapy regimen. No adverse effects that might be attributed to treatment have been observed in any patient. A dTERT-specific immune response has been induced in almost all the treated animals [17,18].

The idiotype of B cell NHL has been intensively investigated for its proven immunogenicity as a promising cancer vaccine in human. Recent findings also indicate that idiotypic vaccines safely and successfully used in additional situations, including in lymphoma patients after high-dose chemotherapy and autologous stem cell transplantation [19].

Regarding human, animal and environmental safety, it is important to remember that variable concentrations of the cytotoxic drugs and their metabolites (i.e. vincristine, doxorubicin and acrolein) are present in dog's urine and may represent a source of exposure for pet owners. Therefore, it is necessary to inform pet owners of this risk and to provide them with chemo-protection guidelines [20].

Finally, canine lymphoma is a spontaneously occurring tumor in dogs that share the same environment as humans and it has a similar clinic presentation. Recently, several spontaneous canine cancers have been proposed as possible models for human tumors because of their similar molecular, biological and clinical characteristics. New therapeutic approaches, such as metronomic chemotherapy, have

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been developed in humans and then applied to dogs and *vice versa* [21,22]. Indeed, metronomic chemotherapy has been successfully used in patients with heavily pretreated, recurrent mantle cell lymphoma [23-25], and in patients with relapsed and refractory, histologically aggressive non-Hodgkin's lymphoma [26,27], suggesting its possible use in dogs also. Metronomic therapy is the application of continuous, low dose chemotherapy (usually cyclophosphamide), offering a novel, less toxic yet effective treatment strategy that inhibits angiogenesis and increases the immune response [28].

In conclusion, the treatment of canine lymphomas may represent an extraordinary opportunity to verify and validate novel therapeutic approaches that can be easily translated to human beings with a mutual benefit for both species.

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