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This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/93415 since

Published version:

DOI:10.1016/j.tvjl.2011.02.017

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19 April 2024

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Canine lymphoma: Going with the flow
The Veterinary Journal, Volume 188, Issue 2, Pages 134–135. May 2011.
http://dx.doi.org/10.1016/j.tvjl.2011.02.017

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Guest Editorial

Canine lymphoma: Going with the flow

Similar to the many forms of non-Hodgkin lymphoma (NHL) described in humans, canine lymphoma represents a morphologically, immunologically and clinically heterogeneous group of neoplasms, so diverse in fact that it has been suggested that the 'one word' diagnosis 'lymphoma' is no longer sustainable (McManus, 2008). The REAL and WHO classifications of human NHL take into consideration multiple features of the disease process (clinical, morphological, immunophenotypic, genetic, epidemiological) that facilitate the identification of the most appropriate therapy and provide the most accurate prognosis. The most recent classifications of canine lymphoproliferative disease, the updated Kiehl and WHO protocols, have taken a step in this direction in more clearly defining tumour sub-types through immunophenotyping (Fournel-Fleury et al., 1997; Valli, 2007).

However, the number of sub-types into which canine lymphoid tumours are classified remains limited (small vs. large cell lymphomas and B vs. T cell lymphomas, respectively) in terms of providing clinically or prognostically useful information. In addition to conventional immunophenotyping, flow cytometric immunophenotyping provides further valuable insights into the character of these neoplasms (Fournel-Fleury et al., 2002; Sozmen et al., 2005; Wilkerson et al., 2005; Comazzi et al., 2006a,b; Riondato et al., 2006a; Gelain et al., 2008). The review by Comazzi and Gelain (2011) in this issue of *The Veterinary Journal*, outlines how, why and when this technique should be deployed in conjunction with cytological evaluation. The authors describe how flow cytometry can provide information in relation to tumour cell lineage, maturation stage and level of antigen expression and highlight the application of this technique in

identifying cell clonality, blood and bone marrow involvement, and in quantifying the numbers of neoplastic cell that survive chemotherapy (minimal residual disease). The review illustrates how such multi-parametric data is invaluable in diagnosing, staging and monitoring canine lymphoma.

Although the advantages of flow cytometry in oncohaematology are acknowledged by many veterinary clinicians, the full potential of the method in clearly differentiating the various sub-types of lymphoma remains to be realised. Recent research suggests we are moving in the right direction with Ponce et al. (2004) describing cytological sub-types that have different prognoses and Marconato et al. (2008) reporting how tumour staging can dictate the chemotherapy protocol. However, to maximise the benefits of such developments, we need to greatly expand the number of tests, such as the flow cytometry, currently available to sub-type canine lymphoma in veterinary diagnostic laboratories.

Studies at The University of Turin are using flow cytometry to investigate if tumour cell DNA content (ploidy and cell cycle), proliferative activity and apoptosis are potentially useful indicators in characterising canine lymphomas and leucaemias. Preliminary findings suggest DNA ploidy and cell cycle analysis with S-phase determination could be useful in discriminating acute from chronic leucaemia and in differentiating acute leucaemia from V-stage lymphosarcoma (Riondato et al., 2010). Flow cytometry is widely used to determine tumour cell DNA content and proliferation in human neoplasms, where these parameters may have use as prognostic markers. DNA aneuploidy has been assessed in both solid tumours and haematological malignancies and a large amount of data exists for this feature in the context of

human breast and colon cancer, as well as for acute lymphocytic leucaemia, lymphoma and multiple myeloma (McCoy and Davis, 2001). Although the results of such studies are often conflicting, the large number of cases where cell DNA content and cell cycle analysis were carried out suggest these parameters are of clinical value in selected tuomours and/or localizations (Bagwell et al., 2001; Michels et al., 2003). Aneuploidy is considered a reliable marker of malignancy (Petrozza et al., 2001) and markers of both ploidy and cell proliferation can facilitate both prognosis and therapeutic strategies (Turner and Wass, 1999). In human NHL, the correlation of DNA ploidy patterns with cytological grading is variable and cell cycle analysis has proved more valuable clinically (Ross, 1996; Pinto et al., 2003). In a veterinary context, few studies have focused on cell DNA content or proliferation in canine lymphomas and small numbers of cases have typically been assessed (Hamilton, 1990; Teske et al., 1993; Rutteman et al., 1994; Guglielmino et al., 2001; Riondato et al., 2006b). Most importantly, these cell parameters have not been correlated with current tumour classification schemes.

Alterations to cell apoptotic mechanisms facilitate both carcinogenesis and tumor progression and also contribute to resistance to treatment as many current anti-cancer therapies rely on the activation of programmed cell death in neoplastic cells. Hence, defects in apoptotic molecules may serve as targets in the design of novel therapeutic strategies as well as biomarkers of response to treatment and prognosis. In this context there may be a role for flow cytometry in the evaluation of apoptotic activity in a neoplasm following cell labelling with annexin V. Research into apoptosis as a therapeutic or prognostic marker of canine lymphoma remains a ‘green-field site’.

The review by Comazzi and Gelain (2011) in this issue of *The Veterinary Journal* clearly outlines the capacity flow cytometry to characterise canine lymphomas and, together with the judicious use of other ancillary tests, will no doubt pave the way to improved patient care. Collaborative research involving both veterinary and human oncologists is likely to be highly mutually beneficial in this context and the recently established research forum[1] co-sponsored by The Universities of Milan and Vienna, is well placed to promote such efforts.

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[1] See: http://www.eu-can-lymph.net

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