Tutorial Article
Equine lymphoma

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Summary
Lymphoma, although rare, is the most common haematopoietic neoplasm encountered in horses and can occur at any age, with horses 4–10 years more commonly affected. Lymphoma can be classified into multicentric, alimentary, mediastinal, cutaneous and solitary. Clinical signs are typically nonspecific until the disease has progressed to end-stage at which time clinical signs reflect function of organ(s) involved. Horses with the cutaneous form of lymphoma typically present with multifocal skin lesions and no other clinical signs. Like the nonspecific clinical signs of lymphoma, results of complete blood count (CBC) and serum biochemistries are not often helpful with diagnosis, but lymphoma should be considered if anaemia, hyperfibrinogenaemia, hyperproteinaemia and hypoalbuminaemia are observed without a clear indication of infectious disease. Identification of neoplastic lymphocytes during cytological examination of a body cavity effusion can confirm the presence of lymphoma. Typically, ante mortem confirmation of lymphoma is made through histopathological examination of a biopsy or cytological examination of a fine needle aspirate of a suspected lesion. Observation of compression or destruction of normal tissue architecture by invading neoplastic cells during histological examination is indicative of lymphoma. Additional diagnostics that may improve our knowledge of equine lymphoma include detection of hormone receptors, immunophenotyping, and immunohistochemical analysis for tumour proliferation rates. Prognosis of horses with lymphoma depends on the form of lymphoma and stage at which the horse is presented but death is the common outcome of this disease. Current treatment options are surgical excision, radiation or administration of chemotherapeutic drugs. Treatment of horses with lymphoma can result in palliation and occasional resolution of this disease. Equine oncology is in its infancy, but through further documentation of horses with lymphoma and their response to therapy, a clearer understanding of the disease process and effective treatment of this neoplasm can be developed.

Introduction
Lymphoma, also known as lymphosarcoma or malignant lymphoma, is a haematopoietic neoplasm arising from lymphoid tissue that includes lymph nodes, spleen and gut-associated lymphoid tissue. Terminology regarding this neoplasm is confusing. Historically the term leukaemia was used to denote a tumour of lymphoid origin. Leukaemia is defined as a cancer arising from the cells of the bone marrow which can result in neoplastic cells in the general circulation. There are leukaemias for every white cell line present in the bone marrow and myelogenous or lymphocytic leukaemias are types of leucocytic leukaemia. Lymphoid leukaemias are the most common type of leucocytic leukaemia. When there is bone marrow affected with lymphoma the terms leukaemic lymphoma or lymphoma with leukaemia are often used to describe this manifestation of the disease.

In human medicine lymphoma is classified as either Hodgkin or non-Hodgkin lymphoma based on a cytological examination of an aspirate or biopsy sample. Although both arise from lymphoid tissue, Hodgkin lymphoma is distinguished from non-Hodgkin lymphoma based on the presence of Reed-Sternberg cells, a giant cell usually derived from B lymphocytes. Non-Hodgkin lymphoma is the most common form of lymphoma identified in domestic animals. Similar to the situation in human medicine following identification of lymphoma, veterinary oncologists attempt to further categorise non-Hodgkin lymphoma by immunophenotyping neoplastic lymphocytes as B cell, T cell or NK cell. This classification allows for diagnosis, disease classification, prognosis prediction, therapeutic selection and monitoring of disease progression.

Incidence and epidemiology
Lymphoma was first reported in a horse in 1858 and is now the most commonly diagnosed haematopoietic neoplasm.

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in horses worldwide (Theilen and Madewell 1979; van den Hoven and Franken 1983). The overall incidence of lymphoma is approximately 1.3–2.8% of all equine tumours and has a prevalence of 0.002–0.5% in the equine population (Savage 1998; Schneider 2003). There is no breed or sex predilection and any age of horse can be affected, but a majority of reported cases are in horses age 4–10 years old. No specific risk factors have been identified and, although there appears to be no genetic predisposition for the development of lymphoma, presence of the neoplasm in an aborted fetus and 2 foals less than 1 year of age have been reported (Tomlinson et al. 1979; Dewes and Blakeley 1980; Haley and Spraker 1983; Seahorn et al. 1988; Savage 1998). Previous reports speculating that malignant transformation of a retrovirus may be a cause of equine lymphoma are questionable because of failure to fulfil Koch’s postulates (Meyer et al. 2006).

**Clinical aspects**

Equine lymphoma is classified into the following clinical syndromes: multicentric or generalised, alimentary, mediastinal, cutaneous and solitary tumours of extranodal sites. Although clinical signs reflect the function of the organ involved and the degree and duration of involvement, common clinical signs for all forms of equine lymphoma include weight loss, depression, lethargy, oedema of the ventral portion of the body wall or distal limb, recurrent fever and lymphadenopathy if peripheral lymph nodes are involved (Neufeld 1973; van den Hoven and Franken 1983; Sweeney and Gillette 1989; Carlson 1995; Savage 1998; McClure 2000; Knottenbelt 2003; Schneider 2003; Meyer et al. 2006; Munoz et al. 2009). Clinical signs of lymphoma typically develop insidiously, but can occur acutely depending on organ involvement. Unfortunately, the diagnosis of lymphoma for most affected horses is late in the course of the disease because of the insidious nature of lymphoma and the lack of pathognomonic clinical signs.

**Multicentric lymphoma**

Multicentric lymphoma, the most common form of equine lymphoma, is characterised by widespread involvement of lymph nodes, peripheral and/or internal, and a variety of organs most likely through distribution of neoplastic lymphocytes via lymphatic circulation (Neufeld 1973; van den Hoven and Franken 1983; Savage 1998; McClure 2000; Knottenbelt 2003; Schneider 2003; Meyer et al. 2006; Munoz et al. 2009). Liver, spleen, intestine, kidney and bone marrow (leukaemic lymphoma) are the organs most commonly affected, but lymphoma of the upper airway, central nervous system, heart, adrenal glands, reproductive organs and eye have also been reported (Madewell et al. 1982; Allen et al. 1984; Browning 1986; Staempfl et al. 1988; Murphy et al. 1989; Held et al. 1992; Freeman et al. 1997; Labelle and De Cock 2005; Stoppini et al. 2005; Germann et al. 2008; Morrison et al. 2008). Clinical signs of multicentric lymphoma reflect the function of organs involved, thus a multitude of symptoms may be present at one time, but horses with the multicentric form of lymphoma commonly have weight loss, oedema of the ventral body wall, elevated temperature, pulse and respiration, and enlarged lymph nodes (lymphadenopathy) (Neufeld 1973; van den Hoven and Franken 1983; Savage 1998; McClure 2000; Knottenbelt 2003; Schneider 2003; Meyer et al. 2006; Munoz et al. 2009). Additional signs of multicentric lymphoma that may be observed include abdominal distension, icterus, malabsorption syndrome, haematuria, or polydipsia and polyuria (Neufeld 1973; Theilen and Madewell 1979; van den Hoven and Franken 1983; Marr et al. 1989; Savage 1998; McClure 2000; Meyer et al. 2006; Munoz et al. 2009). Involvement of the central nervous system results in a variety of neurological signs, depending on the lesion’s location; these signs may include ataxia, cranial nerve deficits, Horner’s syndrome, urinary and/or faecal incontinence or seizures (Neufeld 1973; van den Hoven and Franken 1983; Shamis et al. 1984; Kannegieter and Alley 1987; Zeman et al. 1989; Lester et al. 1992; Morrison et al. 2008; Munoz et al. 2009). Ocular manifestations associated with multicentric lymphoma include intermittent eyelid swelling that may shift from one eye to the other, chronic ocular discharge, oedematous third eyelid, unilateral exophthalmos, corneoscleral masses and chronic uveitis that is unresponsive to treatment (Murphy et al. 1989; Rebhun and Del Piero 1998; Stoppini et al. 2005; Germann et al. 2008). Syndromes such as pseudohyperparathyroidism paraneoplastic pruritis and alopecia also have been reported in horses with multicentric lymphoma (Marr et al. 1989; Finley et al. 1998).

**Alimentary lymphoma**

Approximately 19% of all horses with lymphoma have the alimentary form and, unlike the mean reported age for horses with lymphoma, this type of lymphoma was observed in older horses (mean age of 16 years) (Taylor et al. 2006). The small intestine was more commonly involved than the large intestine, but multiple segments of both small and large intestine also can be affected and lead to involvement of other organs and/or lymph nodes which often makes alimentary lymphoma difficult to differentiate from the multicentric form (Fig 1) (Wilson et al. 1985; Taylor et al. 2006). Alimentary lymphoma is likely to affect multiple segments of intestine in young horses (<10 years) while focal intestinal lesions are often more likely to occur in older horses (Taylor et al. 2006; Munoz et al. 2009). Weight loss, lethargy and anorexia are the most common features of alimentary lymphoma but some affected horses also have abdominal pain and/or diarrhoea caused by malabsorption, along with a protein losing enteropathy (Wiseman et al. 1974; Roberts and
Mediastinal lymphoma

Mediastinal lymphoma, also known as thoracic or thymic lymphoma, is the most common neoplasm of the thorax and has been found in horses of all ages (Mair et al. 1985; Sweeney and Gillette 1989; Mair and Brown 1993). Besides the common clinical signs encountered with all lymphomas, horses with mediastinal lymphoma may also have dyspnoea, coughing and distension of the jugular vein (Mair et al. 1985; Sweeney and Gillette 1989; Mair and Brown 1993). Auscultation of the chest may reveal muffled heart sounds and evidence of pleural fluid can be detected during thoracic percussion and ultrasonography (Mair et al. 1985; Sweeney and Gillette 1989; Mair and Brown 1993). Severe bradycardia caused by complete atrioventricular block associated with mediastinal lymphoma has been reported in one horse (Sugiyama et al. 2008).

Cutaneous lymphoma

Cutaneous lymphoma, an uncommon form of lymphoma, is characterised by multifocal, subcutaneous nodules that may become alopecic, ulcerated and exude a yellow-coloured fluid (Fig 2) (Johnson 1998; Jacobs et al. 2002; Epstein and Hodge 2005; de Brujin et al. 2007). Common locations of cutaneous lymphoma are the head, limbs, trunk and perineum (Gerard et al. 1998; Johnson 1998; Jacobs et al. 2002; Epstein and Hodge 2005; de Brujin et al. 2007). In mares it has been anecdotally reported that the lesions regress during pregnancy but reappear after foaling (Henson et al. 1998; Henson et al. 2000).

Solitary tumours of extranodal sites

Numerous equine case reports document solitary lymphoid tumours. Reported sites of these tumours include the spleen, palate, nasopharynx, nasal passage, sinus, tongue, meninges and pelvis (Lane 1985; Burba et al. 1991; Lester et al. 1992; Tanimoto et al. 1994; Weaver et al. 1996; Gerard et al. 1998; Rhind and Dixon 1999; Montgomery et al. 2009).

Diagnosis

Initial investigation of a horse with suspected lymphoma should include physical examination, palpation of accessible abdominal organs per rectum, CBC and serum biochemistries. Ultrasonographic examination of the thorax and abdomen may aid in locating a mass and the extent of organ and/or localised lymph node involvement (Chaffin et al. 1992; Garber et al. 1994; East and Savage 1998; Roccabianca et al. 2002; Taylor et al. 2006). Aspiration or biopsy of affected lymph nodes or masses is ideal for diagnosis but may be difficult if suspected neoplasia is within the thorax or abdomen. Although cells rarely exfoliate from lymphoma, cytological examination of fluid collected by centesis of body cavities may provide a diagnosis (Mair et al. 1985; Taylor et al. 2006). Laparoscopy or thoracoscopy for biopsy or aspiration or ultrasonographic-guided biopsy or aspiration may be necessary for cytological or histological diagnosis (Pearson et al. 1975; Mair and Brown 1993; Garber et al. 1994; Mair and Hillyer 1997; De Clercq et al. 2004; Pollock and Russell 2006; Taylor et al. 2006).

Horses with lymphoma are usually anaemic as a direct result or combination of premature destruction of antibody coated erythrocytes, inadequate production of erythrocytes due to myelophthisis, anaemia of chronic inflammation and/or blood loss through intestinal ulceration (Neufeld 1973; van den Hoven and Franken 1983; Mair et al. 1985; Savage 1998; Schneider 2003; Meyer et al. 2006; Taylor et al. 2006; Munoz et al. 2009). Erythrocytosis, however, was reported in one horse with lymphoma and attributed to paraneoplastic production of...
erythropoietin (Koch et al. 2006). Although rare, erythrocytosis has also been reported in people and dogs with lymphoma (Koch et al. 2006). Leucocytosis, if present, is a result of neutrophilia, which is likely caused by tumour necrosis (Green and Donovan 1977; Savage 1998; Schneider 2003; Meyer et al. 2006). Rarely is the lymphocyte count increased (Munoz et al. 2009). Although in one report, 14 of 37 horses with lymphoma had lymphocytic leukaemia, it is an uncommon finding except in horses with extensive bone marrow involvement. When affected horses are leukaemic, atypical or abnormal immature lymphocytes are seen during cytological examination of the peripheral blood smear (Fig 3) (Green and Donovan 1977; Gavazza et al. 2003; Tournquist 2008). The abnormal, immature lymphocytes are larger than neutrophils, have increased numbers of nuclei and chromatin that is not densely packed (Tournquist 2008). Other cytological abnormalities reported in the peripheral blood smear of leukaemic horses include Heinz bodies and Sézary cells (medium to large lymphocytes with ceribiform nuclei resembling a monocyt and scant cytoplasm) (Rollins et al. 1991; Polkes et al. 1999). Other blood dyscrasias observed when there is malignant infiltration of bone marrow include thrombocytopenia and pancytopenia (Reef et al. 1984; Roccabianca et al. 2002; Meyer et al. 2006; Kelton et al. 2008). Serum biochemical abnormalities commonly encountered include hyperfibrinogenaemia, hypoalbuminaemia and hyperglobulinaemia (Neufeld 1973; van den Hoven and Franken 1983; Mair et al. 1985; Savage 1998; Meyer et al. 2006; Munoz et al. 2009). Human lymphoma cells were shown to have an increase in production of the cytokine interleukin-6, thus increased concentration of fibrinogen in blood of horses with lymphoma is likely a result of a similar increase in cytokine production by neoplastic lymphocytes (Kato et al. 1998). Hypoalbuminaemia is commonly observed and is most likely a result of a protein losing enteropathy especially in horses with alimentary lymphoma (van den Hoven and Franken 1983; Love et al. 1992; Mair and Hillyer 1997; Meyer et al. 2006; Taylor et al. 2006). Horses with lymphoma of the liver may have decreased production of albumin (Roccabianca et al. 2002; Meyer et al. 2006). A decrease in serum albumin concentration may also be the result of a compensatory reaction to increased serum globulin concentrations, which is likely the result of the immune response to lymphoma antigen (van den Hoven and Franken 1983; Savage 1998; Munoz et al. 2009). Hypercalcaemia when it occurs is claimed to be pathognomonic for a diagnosis of lymphoma but many horses with lymphoma are hypocalcaemic because they are hypoalbuminaemic (Neufeld 1973; Esplin and Taylor 1977; van den Hoven and Franken 1983; Mair et al. 1990; Meyer et al. 2006).

Since IgM deficiency has been associated with equine lymphoma, measurement of serum IgM concentration was claimed to aid diagnosis (Dopson et al. 1983; Furr et al. 1992; Ansar Ahmed et al. 1993; Perkins et al. 2003). People with B cell non-Hodgkin lymphoma typically have decreased production of the majority of immunoglobulin subclasses and this is suspected as the cause for decreased IgM in horses with lymphoma but is unproven (Biggar et al. 2009). One study of horses with lymphoma indicated that, for horses with IgM concentration ≤60 mg/dl, the test had a sensitivity of 50% and specificity of 35% for diagnosis of lymphoma (Ansar Ahmed et al. 1993). However, Perkins et al. (2003) found that when IgM of normal, fit horses was compared to that of horses with lymphoma, an IgM ≤23 mg/dl was more indicative of IgM deficiency. This new value for IgM decreased the sensitivity of the test to 23% but the specificity improved dramatically to 88% (Perkins et al. 2003). Although this new value for normal concentration of serum IgM increases the likelihood of an erroneous ruling out of lymphoma, it is still not a reliable screening test for the diagnosis of equine lymphoma.

Fine-needle aspiration or biopsy (incisional or excisional) of suspected lesions is the preferred method for diagnosis of lymphoma. Tissue samples allow for not only histological diagnosis but also for categorising the lymphoma into B or T cell origin, determining the proliferation rate and presence of hormone receptors. Histological characteristics of lymphoma that distinguish it from lymphoid hyperplasia include compression or destruction of normal tissue architecture, a single population of cells with unorganised chromatin pattern, and variably sized and shaped nucleoli and parafollicular atrophy (Fig 3) (Meyer et al. 2006; de Bruijn et al. 2007; Tournquist 2008). Currently, a histological diagnosis of equine lymphoma is usually the end of an investigation, but further classification, as is done in human oncology, might allow for a more refined prognosis, strategic therapy and therapeutic monitoring. Immunophenotyping is a technique in which lymphoma cells that bare a specific antigen particular to a cell lineage are exposed to marked antibodies for that lineage resulting in a reaction that
identifies the lymphoma type (Kelley and Mahaffey 1998; Gudgin and Erber 2005). Immunophenotyping of neoplastic lymphocytes in horses with lymphoma indicates that multicentric and alimentary lymphomas are predominately T cell origin; mediastinal are almost always T cell origin and cutaneous are of either T cell origin or T cell-rich B cell lymphoma (Asahina et al. 1994; Kelley and Mahaffey 1998; Gavazza et al. 2003; Taylor et al. 2006; de Bruijn et al. 2007; Munoz et al. 2009). This may be unfortunate as T cell origin lymphomas are a more aggressive type of lymphoma and carry a poorer prognosis when compared to B cell lymphomas; however, further investigation into the disease in the horse is warranted (Vail and Young 2002). Another diagnostic tool used by human and small animal oncologists to aid in establishing a prognosis and to monitor response to therapy is determination of tumour proliferation rate by immunohistochemical analysis of antigens associated with the cell cycle (Kelley and Mahaffey 1998). To date this diagnostic tool indicates that both T and B cell lymphomas have high proliferation rates, but until more information is gathered the correlation between the recorded values and prognosis and response to treatment is unknown in horses.

In mares with cutaneous lesions reported to regress during pregnancy, an additional immunohistochemical analysis for progesterone receptors on neoplastic cells may be indicated to offer a possible therapeutic option and to document the prevalence of oestrogen or progesterone receptors in various forms of equine lymphoma. Normal equine lymphoid tissue was determined to contain 1.9% progesterone-positive receptors while lymphomas, especially those rich in B cells, had a high percentage of progesterone-positive receptors (55% overall; 64% in B cell lymphomas, 58% in T cell-rich B cell lymphomas and 33% in T cell lymphomas) and neither normal nor lymphoma tissue was positive for oestrogen receptors (Henson et al. 2000). This study also found that the anatomical location of lymphoma correlated with the percentage of neoplastic cells that had progesterone-positive receptors (100% of splenic lymphomas, 67% of cutaneous, 60% of thoracic, 40% of multicentric and 25% of alimentary of equine lymphomas had progesterone-positive receptors) (Henson et al. 2000). Based on the positive response of women with breast cancer to hormonal management of tumours that has oestrogen or progesterone positive receptors, information needs to be obtained to determine if therapy of horses with either progesterone or anti-progesterone drugs is possible in the management of lymphoma with progesterone-positive receptors (Muss 1992).

As human oncology has progressed and become more sophisticated, the classification for lymphoma has evolved from the Kiel system and National Cancer Institute-Working Formulation to the revised European-American lymphoma system (REAL) to the most recent classification system developed by the World Health Organization (WHO) in 2008 (Armitage 2005; WHO 2008). Unfortunately, lymphoma of domestic animals does not fit neatly into these human classification systems and although the human non-Hodgkin lymphoma working formulation and WHO classification systems have been modified to allow classification of lymphoma for domestic animals, at this time the modified classification systems do not allow for the same predictions of prognosis and therapeutic response as it allows for people (Vail and Young 2002).

**Treatment**

Treatment responses for equine lymphoma are unfortunately unknown since the majority of affected horses are not diagnosed as having the disease until it has reached end-stage. The therapeutic approach to equine lymphoma is similar to companion animals in that the patient’s overall physiological status, extent and location of disease and client’s financial and personal commitment to treatment needs to be evaluated before therapy is begun (Vail and Young 2002; Burns and Couto 2009). Staging the disease may aid in determining what treatment options, if any, may be available (Vail and Young 2002). WHO has developed a clinical staging system for lymphoma in domestic animals based on anatomic site and extent of organ involvement and clinical signs (Table 1) (Vail and Young 2002). Based on clinical stage, options available include surgical excision of solitary tumours, radiotherapy and chemotherapy. However, it is important to remind the owner that therapy is unlikely to be curative but only palliative.

There are several reports describing outcome of horses undergoing surgical excision or reduction of solitary masses of lymphoma involving the large colon, eye and upper airway in the horse (Burba et al. 1991; Dabareiner et al. 1996; Rebhun and Del Piero 1998). There are reports of

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Limited to single node or lymphoid tissue within single organ</td>
</tr>
<tr>
<td>1a</td>
<td>Without systemic signs</td>
</tr>
<tr>
<td>1b</td>
<td>With systemic signs</td>
</tr>
<tr>
<td>2</td>
<td>Involvement of several lymph nodes within a regional area</td>
</tr>
<tr>
<td>2a</td>
<td>Without systemic signs</td>
</tr>
<tr>
<td>2b</td>
<td>With systemic signs</td>
</tr>
<tr>
<td>3</td>
<td>Generalised lymph node involvement</td>
</tr>
<tr>
<td>3a</td>
<td>Without systemic signs</td>
</tr>
<tr>
<td>3b</td>
<td>With systemic signs</td>
</tr>
<tr>
<td>4</td>
<td>Liver or spleen involvement with or without stage 3 disease</td>
</tr>
<tr>
<td>4a</td>
<td>Without systemic signs</td>
</tr>
<tr>
<td>4b</td>
<td>With systemic signs</td>
</tr>
<tr>
<td>5</td>
<td>Manifestation in the blood and involvement of bone marrow and/or other organ systems with or without stage 4 disease</td>
</tr>
<tr>
<td>5a</td>
<td>Without systemic signs</td>
</tr>
<tr>
<td>5b</td>
<td>With systemic signs</td>
</tr>
</tbody>
</table>

*Table 1: World Health Organisation clinical staging system for lymphoma in domestic animals*
surgical resection of the large colon for removal of solitary masses involving the right ventral colon in one horse and left dorsal colon in the other (Dabareiner et al. 1996). The horse that underwent resection of the right dorsal colon was reported to be healthy 18 months following surgery but the other horse was subjected to euthanasia 14 months after surgery because it developed multicentric lymphoma (Dabareiner et al. 1996). Regression of cutaneous lymphoma nodules in a mare was reported following removal of a granulosa theca cell tumour (Henson et al. 1998). For this horse and anecdotally for others, there have been reports of regression of cutaneous form of lymphoma nodules after parenteral administration of synthetic progestin (Henson et al. 1998). For horses with lymphoma of the upper airway, surgical reduction of the mass was only palliative but surgical reduction could potentially be used in conjunction with radiotherapy (Meschter and Allen 1984).

Radiation therapy in the horse is accomplished using one of 2 techniques: brachytherapy or teletherapy. Brachytherapy is the use of a sealed radioactive source (Iridium-92, Iodine-125, or Strontium-90) through implantation or surface treatment of the targeted tissue. Teletherapy is the deployment of radiation from an external beam such as a linear accelerator or cobalt-60 machine. Teletherapy is usually limited to treatment of neoplasia within a distance of 80–100 cm from the radiation source (Henson and Dobson 2004). Whether radiation therapy is possible depends on the volume and location of the lymphoma (Weaver et al. 1996; Vail and Young 2002; Henson and Dobson 2004; Gerard et al. 2010). Typically, teletherapy is employed in treatment of stage I lymphoma or in management of problematic lesions, such as cutaneous lymphoma over an articular surface or perineum (Henson and Dobson 2004). Radiation dose is based on tumour location, size and depth. The total dose of radiation is divided into as few treatments as possible. A decrease in radiation treatments increases normal tissue tolerance and decreases the number of times the patient is placed under general anaesthesia, required for accurate positioning and immobilisation (Henson and Dobson 2004). Side effects of radiation therapy in the horse are localised to the area being treated and include inflammation, ulceration and necrosis which in the case of skin can lead to growth of white hair and temporary regional lymphadenopathy (Weaver et al. 1996; Henson et al. 2004; Henson and Dobson 2004). In a recent report, radiation therapy was used to treat 3 horses with lymphoma, 2 with solitary skin masses and one with a mass in a nasal passage (Henson et al. 2004). These horses were tumour-free for up to 9 years at the time of the report (Henson et al. 2004).

The principles of chemotherapy are to maximise neoplastic cell death while minimising local and systemic effects. Although chemotherapy is often only palliative, curative chemotherapy is possible if a solitary mass is involved. Due to the potential for drug resistance, a multi-drug protocol is often used (Vail and Young 2002). Selection of chemotherapeutic drugs for use in a multi-drug protocol is based on the ability to administer the drugs at the maximum recommended dose based on toxicity, drugs that avoid overlapping toxicities and those that have a known effect against the neoplasm being treated (Vail and Young 2002; Burns and Couto 2009). Several multi-drug protocols have been reported for treatment of equine lymphoma with varying success (Tables 2 and 3) (Gollagher et al. 1993; Saulez et al. 2004; Theon et al. 2007; Burns and Couto 2009). Drug doses for horses can be calculated by using the following formula: body surface area (m²) = wt (g 2/3) × 10.5/10⁴ (Burns and Couto 2009). After beginning chemotherapy, remission of equine lymphoma can be seen within 2–4 weeks and treatment is continued for an additional 2–3 months (Burns and Couto 2009). If remission is still evident after this time and side effects minimal, chemotherapy can be continued. While the lymphoma is in remission, therapy is continued but the intervals between doses of chemotherapeutic drugs is increased by 1 week for 2–3 months then increased by an additional week. This continual therapy has been reported to allow for patients to remain in remission for an additional 6–8 months, but once therapy was discontinued, the lymphoma returned.

**TABLE 2: Chemotherapeutic drugs used in treatment of equine lymphoma**

<table>
<thead>
<tr>
<th>Agent type</th>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agent</td>
<td>Cyclophosphamide</td>
<td>Inhibits DNA, RNA and protein synthesis</td>
<td>Bone marrow suppression, bladder irritation (in canine)</td>
</tr>
<tr>
<td></td>
<td>Chlorambucil</td>
<td></td>
<td>Bone marrow suppression</td>
</tr>
<tr>
<td>Antimetabolides</td>
<td>Cytosine arabinoside</td>
<td>Kills cell in S-phase and blocks progression from G1 to S phase of DNA synthesis</td>
<td>Cardiotoxic, nephrotoxic, potent vesicant</td>
</tr>
<tr>
<td></td>
<td>(Cytarabine)</td>
<td></td>
<td>Perivascular tissue reaction, hepatotoxic</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Doxorubicin</td>
<td>Inhibition of protein synthesis, free radical formation</td>
<td>Laminitis</td>
</tr>
<tr>
<td></td>
<td>Vincristine</td>
<td>Inhibition of intracellular microtubules thus disrupting the cell cycle</td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td>Hormone</td>
<td>Prednisolone</td>
<td>Inhibits DNA synthesis</td>
<td>Can be nephrotoxic in dogs</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>L-asparaginase</td>
<td>Deprives cells of amino acid thus inhibit protein synthesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>Binds DNA strands preventing protein synthesis</td>
<td></td>
</tr>
</tbody>
</table>
COP Cytosine arabinoside 200–300 mg/m² sub cut/i.m. q. 7–14 days
Combo chemotherapeutic
Single drugs Doxorubicin 30–65 mg/m² i.v. (catheter) q. 3 weeks
Single agent therapy L-asparaginase 10,000–40,000 iu/m² i.m. q. 2–3 weeks


TABLE 3: Multi-drug protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
<th>Treatment regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>Cyclophosphamide</td>
<td>200 mg/m²</td>
<td>i.v. (catheter)</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Cytosine arabinoside</td>
<td>1.0–1.5 g/treatment</td>
<td>i.m. or subcut per as</td>
<td>alternating basis daily</td>
</tr>
<tr>
<td></td>
<td>Prednisolone</td>
<td>1 mg/kg bwt</td>
<td>i.v.</td>
<td>q. 7–14 days</td>
</tr>
<tr>
<td></td>
<td>Cytosine arabinoside</td>
<td>200–300 mg/m²</td>
<td>sub cut/i.m. per as i.v.</td>
<td>q. 14 days</td>
</tr>
<tr>
<td></td>
<td>Chlorambucil or</td>
<td>20 mg/m²</td>
<td>i.v.</td>
<td>q. 14–21 days</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide</td>
<td>200 mg/m²</td>
<td>i.v.</td>
<td>q. 48 h</td>
</tr>
<tr>
<td></td>
<td>Prednisolone</td>
<td>1.1–2.2 mg/kg bwt</td>
<td>i.v.</td>
<td>q. 7 days</td>
</tr>
<tr>
<td></td>
<td>Vincristine (can be added if no response initially)</td>
<td>0.5 mg/m²</td>
<td>i.v. (catheter)</td>
<td>q. 2–3 weeks</td>
</tr>
<tr>
<td>Single agent therapy</td>
<td>L-asparaginase</td>
<td>10,000–40,000 iu/m²</td>
<td>i.m.</td>
<td>q. 2–3 weeks</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>200 mg/m²</td>
<td>i.v. (catheter)</td>
<td>q. 2–3 weeks</td>
</tr>
<tr>
<td></td>
<td>or vincristine</td>
<td>0.5 mg/m²</td>
<td>i.v. (catheter)</td>
<td>q. 2–3 weeks</td>
</tr>
<tr>
<td>Combo chemotherapeutic</td>
<td>Autologous tumour vaccine</td>
<td>2 ml injected at 4 sites</td>
<td>i.v. (catheter)</td>
<td>q. 3 weeks</td>
</tr>
<tr>
<td>with autologous vaccine</td>
<td>Doxorubicin</td>
<td>30–65 mg/m²</td>
<td>i.v. (catheter)</td>
<td>q. 3 weeks</td>
</tr>
<tr>
<td>Single drugs</td>
<td>Cisplatin (1 ml of 10 mg/ml cisplatin and 2 ml sesame oil)</td>
<td>1 mg cisplatin/cm² of tumour spaced ~1 cm plane</td>
<td>Intrallesional</td>
<td>q. 2 weeks</td>
</tr>
</tbody>
</table>

Side effects of chemotherapy are not often encountered but include bone marrow suppression, gastrointestinal disturbances, alopecia and laminitis (Vail and Young 2002; Burns and Couto 2009). Thus regular (every 2 weeks) physical examinations and CBC are recommended. If significant abnormalities are observed during physical examination or on CBC, or serum biochemistry evaluation, it may be necessary to delay chemotherapy until those parameters return to within an acceptable range. Options for chemotherapy other than multi-drug protocols include administration of a single chemotherapy drug either systemically or by local injection of a solitary lesion. Doxorubicin has been administered intravenously at a dose of 30–60 mg/m² every 2–3 weeks; however, this drug should be used with caution because myocardial damage and pulmonary fibrosis are potential side effects (Burns and Couto 2009). Intrallesional administration of cisplatin combined with sesame oil at a dose of 1 mg of cisplatin/cm² of tumour injected in planes spaced 1 cm apart repeated every 2 weeks resulted in a success rate of 96.2% for horses with cutaneous lymphoma lesions (Theon et al. 2007).

References


Special Notice for BEVA Members

Further to the Special General Meeting on 10th March 2010 the members voted to make BEVA a company limited by guarantee, to seek charitable status, and to adopt revised Articles of Association. The mechanics of the exercise that followed were the incorporation of a new company, BEVA Ltd, the application for (and award of) charitable status for that company, and the transfer of the Association’s assets and business into that charitable company. The final stage of the process was the dissolution of the old unincorporated association. This process has now been completed. All of the Association’s membership classes have been preserved in the transfer and you will continue to be eligible to receive all of the benefits that you were previously eligible to receive.

If you have questions in relation to the reorganisation, please contact David Mountford at david@beva.org.uk or Deidre Carson via the BEVA office at Mulberry House, 31 Market Street, Fordham, Ely, Cambridgeshire CB7 5LQ. Tel: 01638 723 555.