Coriolus versicolor

Mycotherapy in veterinary oncology

Coriolus versicolor is a medicinal mushroom with numerous properties that is now available in veterinary medicine. Dr Franck Floch will help us to get more information about the uses of PSP in veterinary oncology.

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Cancer is responsible for death in 50% of pets over 10 year of age. Cancer is the main cause of death in dogs, and the second cause of death in cats, following chronic kidney disease, regardless of age. The thesis written by Dr Marie Forterre (Veterinary School of Lyon, France, 2011) mentions that about 27% of owners have ever had a dog or a cat with cancer. Unfortunately, about 50% of owners don't know that anticancer therapies can be used in veterinary oncology; only 38% and 16% of them are aware of chemotherapy and radiation therapy, respectively. However, 90% of them would be interested in considering the use of anticancer treatments for their pets if they were diagnosed with cancer, with 60% of them willing to come to the veterinary hospital several times a month for such a treatment, but 80% of them having some financial limits. The main interlocutor must be the attending veterinarian for owners in case of cancer and anticancer treatments.

The quality of life of cancer-bearing pets must remain the top priority in veterinary oncology. Pet owners are often interested in anticancer treatments in order to improve survival time, in that they are well tolerated and maintain the quality of life of their pets. Conventional anticancer treatments are now widely available in veterinary oncology, mainly with the use of oncological surgery, radiation therapy, chemotherapy, targeted therapies and immunotherapy. More recently, alternative and complementary medicine are of increasing interest to pet owners and care givers, such as herbal medicine or mycotherapy.

Interests of PSP in veterinary oncology

PSP is the main active substance of Versikor$^{500®}$. PSP, a polysaccharopeptide, comes from the COV-1 mycelium strain of the *Coriolus versicolor* medicinal mushroom. This mushroom is used in traditional Chinese medicine for over 2000 years, and is consistently used in China, Japan and Taiwan as an adjuvant to conventional anticancer treatments. PSP is recognized as a biological response modifier, with non-specific immune-stimulating properties, and a direct action on tumor cells and tumor microenvironment. PSP is able to stimulate the immune system of the host and to synergize the effects of some anticancer drugs, thus improving quality of life and survival times of cancer patients.

PSP can act directly on the tumor cells by disrupting the G1/S and G2/M phases of cell cycle progression, and decreasing the number of cells in the S and G2 phase, thus lowering the proliferation rate of tumor cells. PSP is also able to induce apoptosis through upregulation of pro-apoptotic molecules and down-regulation of anti-apoptotic molecules. PSP can also act on the tumor microenvironment, through suppression of enzyme activities and protein levels of matrix metalloproteinases (that are responsible for the degradation of extracellular matrix and basement membrane, a necessary step in neoangiogenesis and metastatic process), and suppression of VEGF (Vascular Endothelial Growth Factor) gene expression. Thus, PSP holds interesting antiangiogenic properties. Finally, PSP can act on the cyclooxygenase-2 (COX-2) expression. COX-2 is a very well-known enzyme that can promote tumor development, through numerous mechanisms of action, and that has been involved in carcinogenesis of mammary carcinoma, transitional cell carcinoma, anal sac carcinoma, or oral squamous cell carcinoma in dogs, for instance. PSP can act as a COX-2 inhibitor, thus leading to decrease in angiogenesis, tumor proliferation, and metastatic process.

PSP can also stimulate the immune system, acting as a non-specific immune-stimulating substance. Cell-mediated immunity is stimulated through increasing in monocytes, macrophages, neutrophils, NK cells, T-cell lymphocytes, CD4+ T-helper lymphocytes, and in the ratio of CD4+/CD8+ T-cells. Humoral-mediated immunity is promoted trough the stimulation of complement component 3 synthesis, and the increased production of pro-inflammatory cytokines, such as Il-2, Il-6, Il-12, TNF-α and IFN-γ. In this way, immunity of the patients is restored for a better fight against cancer. In a recent multicentric non-randomized non-controlled clinical trial conducted in veterinary oncology, dogs diagnosed with unresectebale, incompletely excised or metastatic solid tumors were prospectively included to be treated with PSP alone (Versikor$^{500®}$, dose of 100 mg/kg/day) over a 50-day period, without any concurrent medication. Between Day 0 and Day 50 of this study, an increase in serum IFN-γ, TNF-α and Il-2 levels was reported in 83%, 75% and 85% of the included dogs, respectively. Similarly, a non-significant increase in the lymphocyte counts was observed between Day 0 (median = 1500/mm^3) and Day 50 (median = 1910/mm^3), thus supporting the preliminary results of human studies.

Impact of PSP on quality of life and overall survival

To date, few studies are available in veterinary medicine concerning *Coriolus versicolor* and quality of life in cancer-bearing dogs and cats. Thus, most available scientific evidence comes from human literature. PSP has been demonstrated to decrease adverse effects of chemotherapy and radiation therapy, but also clinical signs related to tumor progression, such as weakness, anorexia, nausea, vomiting, weight loss or pain symptoms. In the recent canine clinical trial described above, quality of life and appetite were maintained throughout the study between Day 0 and Day 50, with weight and rectal temperature stabilization, absence of hematological or biochemical toxicity, absence of clinical adverse effects, and a significant decrease in the discomfort induced by the tumor between Day 0 and Day 21 (p = 0,02).

A recent meta-analysis of randomized, placebo-controlled, double-blinded clinical trials regarding breast, gastric and colorectal cancer treated with chemotherapy in human oncology reports a 9% absolute reduction in the 5-year mortality and 1 additional patient alive for every 11 patients treated with PSP, showing a strong benefit of PSP on overall survival in human cancer patients.

Finally, PSP may present a synergistic action with chemotherapy in increasing the cytotoxicity of doxorubicin and etoposide in human tumor cell lines, and in reducing the immunosuppressive effect of chemotherapy, mainly cyclophosphamide.

In veterinary oncology, only one scientific study is available and published in the context of splenic hemangiosarcoma in dogs (Brown et al. 2012). Splenic hemangiosarcoma is a very aggressive and highly metastatic malignant tumor, whose prognosis is poor despite surgery and adjuvant chemotherapy (Table 1). This double-blinded randomized multi-dose study included 15 dogs diagnosed with a splenic hemangiosarcoma (with or without distant metastasis at diagnosis), and treated with various doses of PSP following splenectomy: 25, 50 or 100 mg/kg/day, without any concurrent medication. No adverse clinical signs or hematological or biochemical toxicity were reported. A daily dose of 100 mg/kg/day of PSP has been shown to significantly delay the onset or progression of abdominal metastasis (DFI = 112 days *vs* 30 days at the dose of 25 mg/kg/day). Moreover, a non-significant but dose-dependent increase in the median survival time was also observed: 199 days for 100 mg/kg/day, *vs* 117 days for 50 mg/kg/day, and only 30 days for 25 mg/kg/day. The use of PSP as an adjuvant to splenectomy for canine hemangiosarcoma leads to one of the best median survival times reported in the veterinary literature following the use of doxorubicin – dacarbazine cytotoxic chemotherapy (> 550 days, Finotello et al. 2017) and the association of metronomic and doxorubicin-based cytotoxic chemotherapy protocols (not reached, Finotello et al. 2017). Since this first study of Brown et al., two additional case reports were published with the adjuvant use of PSP in a dog with cardiac hemangiosarcoma (Arai et al. 2019) and in a dog with splenic hemangiosarcoma and ocular metastasis (Chaikin et al. 2018).

In veterinary oncology, the use of Versikor$^{500®}$ may be of value to cancer-bearing dogs and cats:

- In addition to conventional anticancer therapies, concurrently or sequentially, in particular cases of malignant and aggressive tumors with a high metastatic risk.
- When owners decline conventional anticancer treatments.
- When conventional anticancer therapies do not improve overall survival or quality of life.
- When the overall health condition of the patient may prohibit the use of conventional anticancer treatments (such as chronic cardiac or renal disease).
- When the owner is interested in alternative and complementary medicine.

Naturopaths also believe in the immunotherapeutic properties of PSP in case of immune diseases, such as retroviral infections in cats (FIV/FeLV), atopic dermatitis, feline coryza syndrome, feline chronic gingivostomatitis, autoimmune diseases, idiopathic inflammatory bowel disease…

Versikor$^{500®}$ is a feed supplement for cancer-bearing dogs and cats that is rich in PSP (> 38% polysaccharides and > 11,5% peptides). Versikor$^{500®}$ is available in boxes of 60 or 180 tablets, that are scored and highly palatable ("liver flavor"). The dose of 100 mg/kg/day is recommended, that means 1 tablet of 500 mg for 5 kg of body weight, for a long-term oral administration. Versikor$^{500®}$ is already available in the entire French central purchasing groups, and can also be directly ordered from the Sum Lab Vet laboratory (www.versikor500.com or contact@sumlabvet.com).

PSP extracted from the *Coriolus versicolor* medicinal mushroom represents a new therapeutic option of value to cancer-bearing dogs and cats, as an adjuvant to conventional anticancer therapies. PSP can also be used alone in the palliative setting when conventional anticancer treatments are declined, whatever the reasons may be, in order to improve quality of life, maintain adequate weight and appetite, stimulate the immune system, and maintain a positive link with owners and their pets, while avoiding side effects and toxicity.

Surgery	Adjuvant treatment	References	Median survival time
Splenectomy	None	Johnson et al. 1989 Wood et al. 1998 Wendelburg et al. 2015	19-86 days
Splenectomy	Doxorubicin (+/- cyclophosphamide)	Sorenmo et al. 1993 Vail et al. 1995 Ogilvie et al. 1996 Finotello et al. 2017 Alexander et al. 2019 Treggiari et al. 2020	141-180 days
Splenectomy	Doxorubicin + vincristine + cyclophosphamide	Hammer et al. 1991	172 days
Splenectomy	Epirubicin	Kim et al. 2007	144 days
Splenectomy	Doxorubicin, then toceranib	Gardner et al. 2015	172 days
Splenectomy	Metronomic chemotherapy (cyclophosphamide, COX-2 inhibitor, +/- etoposide)	Lana et al. 2007 Treggiari et al. 2020	178-225 days
Splenectomy	Anthracycline / Lomustine	Moore et al. 2017	158 days
Splenectomy	Doxorubicin + dacarbazine	Finotello et al. 2017	> 550 days
Splenectomy	PSP	Brown et al. 2012	199 days
Splenectomy	Doxorubicin-based protocol, then metronomic chemotherapy	Finotello et al. 2017 Alexander et al. 2019 Treggiari et al. 2020	212 days - not reached

Table 1: Published median survival times depending on treatments used in canine splenic hemangiosarcoma