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Enhanced therapeutic effect of APAVAC immunotherapy in combination with dose-intense chemotherapy in dogs with advanced indolent B-cell lymphoma

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ABSTRACT

The aim of this non-randomized controlled trial was to compare time to progression (TTP), lymphoma-specific survival (LSS), and safety of an autologous vaccine (consisting of hydroxyapatite ceramic powder and Heat Shock Proteins purified from the dogs' tumors, HSPPCs-HA) plus chemotherapy versus chemotherapy alone in dogs with newly diagnosed, clinically advanced, histologically confirmed, multicentric indolent B-cell lymphoma. The vaccine was prepared from dogs' resected lymph nodes and administered as an intradermal injection. Forty-five client-owned dogs were enrolled: 20 dogs were treated with dose-intense chemotherapy, and 25 received concurrent immunotherapy. Both treatment arms were well tolerated, with no exacerbated toxicity in dogs also receiving the vaccine. TTP was significantly longer for dogs treated with chemo-immunotherapy versus those receiving chemotherapy only (median, 209 versus 85 days, respectively, $P = 0.015$). LSS was not significantly different between groups: dogs treated with chemo-immunotherapy had a median survival of 349 days, and those treated with chemotherapy only had a median survival of 200 days ($P = 0.173$). Among vaccinated dogs, those mounting an immune response had a significantly longer TTP and LSS than those with no detectable response ($P = 0.012$ and $P = 0.003$, respectively). Collectively these results demonstrate that vaccination with HSPPCs-HA may produce clinical benefits with no increased toxicity, thereby providing a strategy for enhancing chemotherapy in dogs with advanced indolent lymphoma.

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1. Introduction

In humans and dogs, indolent lymphomas represent a group of incurable slow-growing tumors, characterized by a continuous relapse pattern, for which there are no defined first-line therapies [1]. The biologic behavior is extremely variable, with some patients having an aggressive course and death within a few months despite intense treatment, and others living for years, never requiring therapy [2–7].

While in most cases indolent lymphoma is discovered incidentally and harbors a good prognosis [5–7], emerging data support that some dogs experience pathological and clinical progression [2].

A universally accepted definition of "advanced" lymphoma does not exist; nevertheless, it is reasonable to reserve the term

Abbreviations: BM, bone marrow; B-SLL, B-cell small lymphocytic lymphoma; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; DTH, delayed-type hypersensitivity; FC, flow cytometry; FL, follicular lymphoma; HSP, heat shock protein; HSPPC, heat shock protein-peptide complex; LDH, lactate dehydrogenase; LN, lymph node; LSS, lymphoma-specific survival; MRD, minimal residual disease; MZL, marginal zone lymphoma; PARR, polymerase chain reaction for antigen receptor rearrangement; PB, peripheral blood; PCV, packed cell volume; PD, progressive disease; PLT, platelets; PR, partial remission; TTP, time to progression; VCOG-CTCAE, Veterinary Co-operative Oncology Group – Common Terminology Criteria for Adverse Events; WHO, World Health Organization.

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"advanced" for stage IV–V patients, with disease bulk or symptoms [2]. With this premise in mind, it comes as no surprise that the treatment of this disease is controversial. As a rule, an advanced WHO clinical stage (IV–V) and the presence of symptoms typically speak in favor of undertaking treatment. Although chemotherapy is believed to improve remission duration and survival, the disease is essentially incurable [3].

Cancer therapeutic vaccines are a promising yet challenging strategy. The past two decades have witnessed approaches to incorporate active immunotherapy into the multimodal care of veterinary oncology patients for whom there continues to be unmet medical need [8–14].

Tumor-derived HSPPC coupled with hydroxyapatite has recently proven to induce immunity against autologous tumors in a clinical trial on canine DLBCL, ultimately translating into clinical efficacy [13].

A component of HSPPC, HSP, functions as protein chaperone, aimed at stabilizing its associated molecules when the cells undergo stress situations. Cancer cells synthesize high amounts of HSPs [15]. The immune response induced by an HSP-based vaccine begins with antigen-presenting cells taking up antigenic epitopes with HSP and presenting them on major histocompatibility complex class-I molecules [15–17]. Presented epitopes are then recognized by CD8 T-cells and activate the cellular immune response.

Thus, by purifying the cancer HSPs and by associating these molecules to an adjuvant, a vaccine against specific antigens of the tumor cells is obtained [13,15–17]. Hydroxyapatite shows adjuvant properties, and HSPs have an affinity for its surface, thereby facilitating purification using hydroxyapatite powder columns [18].

Based on the encouraging results obtained in dogs with DLBCL, a clinical trial was carried out to evaluate the efficacy and safety of autologous HSPPC-vaccine in combination with chemotherapy as the primary treatment for dogs with newly diagnosed, advanced indolent B-cell lymphoma.

2. Materials and methods

2.1. Study design

This study was designed as a prospective, controlled, non-randomized, bi-center trial to investigate TTP and LSS (primary endpoints) and safety (secondary endpoint) of chemotherapy (Group 1) in comparison with chemo-immunotherapy (Group 2).

2.2. Inclusion criteria

Dogs were recruited at the Centro Oncologico Veterinario and the Department of Veterinary Science and Public Health (University of Milan) between 2011 and 2014. To be eligible for recruitment, dogs were required to have untreated, histologically confirmed, indolent B-cell lymphoma (i.e., FL, B-SLL, or MZL) of advanced (IV–V) clinical stage.

Included dogs were required to undergo a complete staging work-up [19,20]; Supplemental Data]. The cut-off for PB and BM infiltration was set at >0.9% of medium/large CD21+ cells recognized as neoplastic because of larger size and/or different fluorescence intensity compared to normal circulating B-cells [21].

All dogs also were required to undergo lymphadenectomy to confirm pathology [22], and provide material for the vaccine generation.

Ineligibility criteria included concurrent serious disorder (active systemic infection or second malignancies) that, in the opinion of the clinician, would compromise the ability to adhere to the protocol, previous therapy with any chemotherapeutic or immunotherapeutic agent, or glucocorticoids within the last 60 days.

The care of the dogs enrolled in the study was in accordance with institutional guidelines. All owners provided written informed consent.

2.3. Vaccine preparation

HSPPC was purified from LN specimens and prepared as a vaccine. The method of preparation is described in detail elsewhere [13]; Supplemental data]. Once prepared, the doses were kept frozen at −18 °C until use.

2.4. Treatment

Dogs in both treatment groups received the same 20-week combination chemotherapy, consisting of L-asparaginase (week 1), vincristine (week 2, 3, 4, 13), cyclophosphamide (week 2, 13), doxorubicin (week 7, 16), lomustine (week 10, 19), and prednisone (week 1 through 20), as previously described [13].

Dogs whose owners wished to pursue immunotherapy also received an intradermal injection of 0.5 ml vaccine on weeks 4–7, 12, 16, 20, and 24. The injection areas were shaved and aseptically prepared prior to vaccine administration. Vaccines were administered utilizing a 22 gauge needle that was 0.7 mm × 30 mm in length. For 30 min after the first injection, each dog was monitored for signs of skin irritation; vital signs were recorded before the injection and just before the dog left the clinic. All owners were asked to record and report adverse effects upon their visit for the next vaccine administration or to immediately report by telephone if serious events occurred.

Safety was assessed at each scheduled treatment session using the VCOG-CTCAE criteria [23]. Treatment was delayed for a maximum of 1 week or dose was decreased by 20% for safety changes. Concomitant medications, including antibiotics, antiemetic and antidiarrheal, were permitted to manage adverse events.

2.5. Response assessment and follow-up

Response was evaluated at each treatment session according to previously published criteria [24]. Responses were required to last for at least 28 days.

Two weeks after having completed chemotherapy and following immunotherapy, if administered, all dogs underwent restaging by repeating the initially altered examination. For MRD monitoring, FC on PB, BM and a LN aspirate, and/or PARR on PB, BM and LN obtained from a second lymphadenectomy was carried out [25]. Dogs were then rechecked through monthly physical examinations during the first year, and every other month thereafter. Dogs having initially visceral, PB and/or BM involvement also underwent imaging or FC testing every three months. Also, owners were asked to immediately seek for medical consultation in case of symptoms occurrence or LN enlargement.

Relapse was defined as clinical reappearance and cytological evidence of lymphoma in any anatomical site in dogs having experienced CR, whereas relapse for animals with PR was defined as progression.

Dogs that relapsed during or after the treatment protocol were offered standardized rescue chemotherapy.

2.6. Immunological monitoring

In vivo immune responses were documented in vaccinated dogs by performing DTH skin tests and by evaluating the local inflammatory response after the eighth vaccination (Supplemental data)

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