The 4th Pillar of Veterinary Cancer Treatment: Immunotherapy

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Introduction

We are constantly hearing about new immunotherapies to help treat cancer in humans. From different cell therapies to monoclonal antibodies, immunotherpeutics have become another treatment option in the arsenal against cancer.[1] However, it's time to hear more about utilizing immunotherapy to treat cancer in veterinary medicine.

There are millions of new companion animal cancer diagnoses in the US each year and a recent study highlighted that the majority of pet owners would never pursue chemotherapy to treat their pet after a cancer diagnosis.[2] Immunotherapies represent another option for pet owners to consider that have a lower risk profile that may be appealing to pet owners. In this lecture, we will cover immune checkpoint inhibitors and cancer vaccines as potential therapeutic treatment options after a pet is diagnosed with cancer.

Cancer and the immune system

Cancer is a disease of the immune system. Genetic mutations, environmental factors and tumor microenvironment modifications result in the immune system's inability to recognize and destroy neoplastic cells. These mutations start at the DNA level, but result in the translation of proteins on the surface of the tumor cell that are different than normal, healthy, self-proteins. These tumor-associated and tumor specific neoantigens are novel proteins found on the surface of the tumor cell.[3] These mutations may allow a neoplastic cell to divide unregulated and evade immune detection. However, when that tolerance is broken, the immune system is able to come in and complete its job.[3] Ways of overcoming that immunotolerance include depleting T_{reg} cells by using metronomic chemotherapy, utilizing checkpoint inhibitors, cytokine therapies or administering therapeutic cancer vaccines.

Checkpoint or Checkmate?

Checkpoint inhibitors are a class of monoclonal antibodies that act to keep CD8+ cytotoxic T-cells active inside of the tumor microenvironment. Through common mutations associated with certain cancers, certain tumors may evolve proteins on the surface of the cell that when a T-cell approaches the tumor cell to kill it, the tumor can put the T-cell into a senesced or "sleep" state.

These proteins like programmed death ligand 1 (PD-L1) or cytotoxic T lymphocyte antigen 4 (CTLA-4) can be blocked by utilizing a checkpoint inhibitor to ensure that the tumor cell and the T-cell do not bind allowing the T-cell to remain active and do its functional job that its meant to do—kill the tumor cell. On the human side, there are nearly 10 checkpoint inhibitor monoclonal antibodies approved that can help more than 19 different cancer types.[4]

However, its rare that these therapies work as a monotherapy. Patients have to be screened to understand their overall expression of the protein and depending on the tumor, combination with chemotherapy, radiation therapy or other immunotherapies can be considered.[4] Additionally, its nearly impossible to understand the patient's ability to form a strong enough T-cell immune response at the onset of the therapy. Regardless, immune checkpoint inhibitors have become standard of care for tumors like melanoma and non-small cell lung carcinoma with some patients experiencing curative intent.[5]

In the veterinary market, Merck is releasing a PD-1 checkpoint inhibitor (Gilvetmab) for canines with melanoma or mast cell tumors (MCT). This is a 'caninized' monoclonal antibody that ensures binding to the PD-1 receptor and effective blocking of the interaction between the tumor and T-cell. Gilvetmab is administered intravenously over 30 minutes and they have been able to show that for MCTs 73% of patients had an objective response or stable disease and in melanoma, 60% of their patients had an objective response or stable disease.[6]

So, the goal of a checkpoint inhibitor is to put the cancer in check by the CD8+ T-cells—checkmate indeed!

Cancer Vaccines

Cancer vaccines can be preventative or therapeutic in nature. Preventative cancer vaccines like Guardasil® are meant to stop the inflammatory process of the human papilloma virus remaining unchecked and prevent the potential formation of cervical cancer in women who are genetically predisposed.

Cancer vaccines can be therapeutic—meaning that they are utilized after a patient has been diagnosed with cancer and the goal of the vaccine is to stimulate an immune response against applicable antigens to ensure that T-cells have memory and are armed to kill the cell that is expressing that foreign protein.

Autologous cancer vaccines are a form of active cancer immunotherapy a tumor is surgically excised and submitted in to a centralized lab. Once there, the patient's antigenic material is processed *ex vivo* and returned to the patient with the goal of stimulating both a humoral and cell-mediated immune response against multiple known and unknown tumor-associated and tumor-specific antigens. Rather than relying on a single antigen, the goal is to stimulate a response that is truly representative to the patient's own cancer and mutational profile.

Autologous cancer vaccines have several potential advantages over conventional cancer therapy. They have been associated with fewer, and less severe adverse events in veterinary patients and the course of therapy may be shorter than chemotherapy.[7-9] The cost for treatment is often less, particularly when considering the attendant costs of managing adverse events with chemotherapy or radiation therapy. Lastly, autologous cancer vaccines are tumor-type and species agnostic and may be useful against a wide variety of solid tumors. Despite these advantages, a number of challenges with this approach have also been identified, such as the need for large, statistically valid longitudinal placebo-controlled studies. [10] These large and long-lasting clinical trials are

difficult to run on patients that may benefit most from an autologous therapy: patients with early-stage disease.

Synergistic combinations

As with any cancer treatment plan, combining modalities is likely to yield more promising results than relying on a single method alone. Two commonly used chemotherapy approached metronomic chemotherapy and high-dose chemotherapy are effective at depleting T_{reg} cells. T_{reg} cells are considered the 'bad actors' of the immune system as it relates to cancer because their job is to suppress an immune response. The more we can eliminate immunosuppressive T_{reg} cells the higher likelihood we will have at ensuring the CD8+ T-cells are active in the microenvironment when we need them.

In canine patients with lymphoma, a compelling example emerges when chemotherapy is combined with an autologous cancer vaccine. In a randomized trial, dogs receiving this combination demonstrated a significantly extended median survival time (505 days) compared to those receiving chemotherapy alone (159 days) ($p = 0.0018$).[11]

Moreover, preclinical rodent models have underscored the potential synergy between autologous cancer vaccines and radiation therapy, suggesting this approach could be adapted effectively for veterinary cancer patients.[12] Last, the combination of immune checkpoint inhibitors and autologous cancer vaccines represent an ideal combinatorial strategy when the majority of the tumor mass still remains after surgical excision. Particularly, in the case of canine gliomas, a study was run evaluating a novel CD200 inhibitor where patients who received the immune checkpoint and autologous vaccine survived the longest.[13]

In essence, exploring these immunotherapy combinations holds great promise in advancing the treatment options available to veterinary patients battling cancer.

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