

Immunotherapy for canine cancer

Liangyifei Li *

Nanning No.14 Middle School, Guangxi, China

* Corresponding author: 2569460075@qq.com

Abstract. Cancer in dogs is a serious and prevalent disease that has drawn significant attention in the field of veterinary medicine, representing the most common cause of death in adult dogs. Traditional treatments such as chemotherapy and surgery have many limitations and side effects and have not been able to completely eliminate cancer, and challenges still remain in improving the survival rate and life quality in dogs. The development of a new therapeutic methodology for canine cancer to improve treatment effectiveness and survival rate has become the focus of many scientists. Immunotherapy, as a new treatment strategy, is one of the important research directions in the field of cancer treatment in canine animals. Adoptive T-cell therapy, checkpoint inhibitors, and oncolytic virus therapy, as important immunotherapy approaches, have shown promising treatment effects. This article will introduce the background of canine cancer, the background of immunotherapy, and discuss the application prospects of adoptive T-cell therapy, checkpoint inhibitors, oncolytic virus therapy, and other related topics in the treatment of canine cancer.

Keywords: Canine cancer, Immunotherapy, Adoptive T-cell therapy, Checkpoint inhibitors, Oncolytic virus therapy.

1. Introduction

Canine cancer refers to malignant tumors that occur in dogs. In recent years, with the increase in the number of pet dogs and the change in dog-keeping concepts, the incidence of canine cancer has been on the rise. In a retrospective study examining canine mortality, it was shown that cancer accounted for the highest proportion of deaths, with an estimated prevalence of 30% [1-3]. The causes of canine cancer are diverse, including genetic factors, environmental factors, dietary habits, etc. Among them, genetic factors are considered to be one of the most important factors in the occurrence of canine cancer. Certain dog breeds are more prone to specific types of cancer, which are related to their genetic genes. There are various types of cancer in dogs, including non-Hodgkin lymphoma, malignant melanoma, osteosarcoma [OSA], hemangiosarcoma, and mammary tumors, among others. These cancers exhibit different clinical manifestations. Some symptoms are more obvious, such as lumps, ulcers, and difficulty breathing, while others are more subtle, like loss of appetite and weight loss. Canine melanoma is characterized by a high degree of malignancy and exhibits resistance to therapeutic interventions. Melanomas arise from melanocytes. The identification of melanomas presents a considerable challenge due to their potential resemblance to various other tumor forms, including carcinomas, sarcomas, lymphomas, and osteogenic tumors [4, 5]. Hemangiosarcoma (HSA) is a malignancy characterized by its very aggressive nature and its origin in the vascular system. This particular type of malignancy is highly prevalent in the spleen and is responsible for non-traumatic abdominal bleeding in canines [6]. Non-Hodgkin lymphoma (NHL) is a collection of malignancies that exhibit a wide range of lymphocyte proliferations, making it a prevalent neoplasia in both humans and pet dogs [7, 8]. Osteosarcoma is the prevailing main bone neoplasm identified in canines. The majority of instances of canine osteosarcoma (OSA) are observed in the appendicular skeleton [9]. However, it is worth noting that axial sites, including the skull, mandible, maxilla, and extracranial flat and irregular bones (such as vertebrae, ribs, sternum, scapula, or pelvis), are also frequently reported [10-13]. Furthermore, there have been several confirmed occurrences of extra-skeletal obstructive sleep apnea (OSA) in companion animals [14]. Canine mammary tumors, known as breast cancer, have a rather high prevalence in dogs. The majority of these neoplasms are classified as carcinomas. Mammary tumors typically originate as a palpable mass located in the abdominal region proximal to the canine's mammary glands. The presence of several tumors might give rise to a

sequential arrangement of neoplastic growths along the mammary glands. Additionally, it has been observed that this phenomenon can lead to the expansion of adjacent lymph nodes [15]. If discovered and treated early, some canine cancers can be cured. However, due to the early symptoms of canine cancer often being overlooked or confused with other diseases, many dogs are already in advanced stages when diagnosed, making treatment challenging. To better prevent and control canine cancer, people are paying increasing attention to the health management of dogs. Regular health check-ups, a proper diet, appropriate exercise, and avoiding exposure to harmful substances all help reduce the incidence of canine cancer. In addition, researchers are actively exploring new treatment methods such as chemotherapy, radiation therapy, and immunotherapy to improve the treatment effectiveness and survival rate of canine cancer. Canine cancer immunotherapy is an important research direction in the field of cancer treatment for canine animals. In canine cancer immunotherapy, the mechanism of action of the immune system is mainly utilized. The immune system is an important defense mechanism in humans and animals, which recognizes and eliminates abnormal cells, including cancer cells. Immunotherapy achieves the effect of treating cancer by activating the host immune response and enhancing the ability of immune cells to attack tumors. There is extensive research behind canine cancer immunotherapy. Through experimental and clinical observations, researchers have found that using immunotherapy can significantly improve the cure rate and survival of canine cancers. The discovery has attracted increasing interest from scientists who are working to develop new immunotherapies, including adoptive T-cell therapy, oncolytic virus therapy, checkpoint inhibitors, and more. Research on canine cancer is not only of significant importance for the health of dogs but also has invaluable implications for human health studies. Many types of canine cancer share similarities with human cancer, including the mechanisms of onset, disease progression, and treatment response. Therefore, studying canine cancer can provide valuable insights and references for the prevention and treatment of human cancer.

In conclusion, canine cancer, as a common pet disease, has great implications for canine health and human disease research. By strengthening precautions, improving early diagnosis, and developing effective treatments, we can better protect dogs and promote the development of human medicine.

2. Adoptive T-cell therapy

Adoptive T-cell therapy is an emerging therapeutic approach for cancer and other immune-related diseases. It uses a recombinant T-cell receptor [TCR] or a chimeric antigen receptor [CAR] to enhance the patient's own immune system. Adoptive T-cell therapy enables T-cell-enhanced immune responses to target specific antigens or tumor cells by changing the genetic information of the patients' genetic profile [16]. The rationale for adoptive T-cell therapy is based on the following several steps: First, the physician will take a T-cell sample from the patient's blood. These T-cells will be processed by the laboratory for genetic engineering to express a specific TCR or CAR. These TCRs or CARs are able to recognize and bind specific antigens, such as tumor-associated antigens. Next, the modified T-cells were expanded in the laboratory to obtain sufficient numbers. Finally, these modified T-cells will be re-infused into the patient. When the modified T-cells are reinfused into the patient, they further activate the immune response by recognizing and binding to specific antigens. Once the antigen is identified, modified T-cells release cytotoxic substances such as cytokines and perforin to kill cancer cells or infected cells. Adoptive T-cell therapy in canine cancer is a novel anticancer therapy based on extracting T-cells from infected dogs and transforming their genes into anticancer T-cells [17]. In this way, the immune system of the affected dogs can become more powerful to effectively combat the growth and spread of cancer cells. The advantages of adoptive T-cell therapies are their high specificity and selectivity and their ability to attack specific antigens or tumor cells without damaging normal cells. The clinical application of adoptive T-cells in canine cancer has achieved remarkable results. Through several studies and clinical trials, this therapy has found significant efficacy for some types of canine cancer, which can effectively prolong

the survival of infected dogs and improve the cure rate. Furthermore, adoptive T-cell therapy in dogs can also reduce pain and discomfort and improve their quality of life. However, adoptive T-cell therapies still face some challenges. On the one hand, is how to improve efficacy and safety, as overactivated immune responses can cause serious side effects such as cytokine release syndrome and open viral infection. On the other hand, the preparation and production of adoptive T-cell treatments also face several technical challenges, including how to select the most appropriate TCR or CAR and how to improve the efficiency of T-cell expansion. Moreover, the development and application of adoptive T-cell therapy technology in canine cancer still needs the support of more scientific strength and clinical practice. Meanwhile, the high cost of adoptive T-cell therapy in canine cancer also limits its application in clinical promotion. Adoptive T cell therapy is an emerging field of investigation in both human and canine populations. T-cell treatments have been employed in the treatment of many tumor histologies in humans, encompassing lymphoma, melanoma, and colon cancer. While the current application of this approach is limited to lymphoma, ongoing research is exploring its potential for other types of cancers. There exist numerous techniques that can be employed to harness the cell-mediated anticancer characteristics exhibited by T cells. Several clinical trials have provided evidence of the notable effectiveness of this therapeutic approach in addressing specific forms of cancer, including hematological malignancies like acute lymphoblastic leukemia and NH. Additionally, adoptive T-cell therapy has shown promise in treating specific autoimmune diseases, including conditions like rheumatoid arthritis and multiple sclerosis [18, 19].

In adoptive T-cell treatment of canine cancer, it is necessary to extract T-cell s from affected dogs. This is usually achieved by T-cell separation techniques in the peripheral blood. Next, after a series of in vitro manipulations, including activation, amplification, and gene modification steps, the T-cell s are transformed into T-cell s with specific anticancer specificity. These modified T-cell s are called CAR T-cell s [chimeric antigen receptor T-cell s]. CAR t cells are re-injected into affected dogs, and these cells are able to recognize and attack cancer cells to achieve therapeutic efficacy. CAR T-cells seek in the body and bind to cancer cells, which then release cytotoxins that destroy cancer cells. The results show that this treatment avoids the damage to normal cells caused by conventional chemotherapy and improves the treatment effect [20, 21].

3. Oncolytic virus therapy

Oncolytic virotherapy is an emerging treatment for cancer with principles based on the use of specific viruses to selectively infect tumor cells and cause their death. The goal of this therapy is to reduce the damage to normal cells by selectively killing cancer cells. Detailed instructions for oncolytic virotherapy can be divided into several key steps. First, suitable viral strains were selected as the oncolytic viral vectors. These viruses are often genetically engineered for their ability to specifically infect tumor cells and reproduce within them. Next, the oncolytic viruses need to be directed to the tumor tissue. This can be achieved by direct injection of the virus into the tumor site or by systemic delivery. Targeted oncolytic viruses are made by linking the recognition fraction of specific tumor-associated antigens to viral particles. In this way, the oncolytic virus is able to enter the tumor cells more efficiently. Once the oncolytic virus enters the tumor cells, it begins to multiply and infect other cancer cells. This infectious process leads to the death of tumor cells, releasing more oncolytic viruses to further infect the surrounding cancer cells. At the same time, the infection process will activate the immune system, triggering the body's immune response to tumors. Finally, oncolytic virotherapy also needs to consider post-treatment monitoring and support. Patients need regular examinations during treatment to assess the efficacy of oncolytic virotherapy. Furthermore, patients may need to receive other therapeutic methods, such as chemotherapy or radiotherapy, to further improve efficacy [22-24]. In oncolytic virotherapy, the virus is modified into vectors with the ability to selectively kill tumor cells. These modified viruses are able to infect tumor cells and replicate and spread within them, eventually leading to the death of tumor cells without causing significant damage to normal cells. Compared with conventional radiotherapy and chemotherapy, oncolytic virus therapy

has many advantages, such as a high therapeutic effect, lower toxic side effects, and less drug resistance, which brings new hope for cancer treatment. Oncolytic virotherapy still faces some challenges, such as the selection of suitable oncolytic viral vectors and the problem of effective delivery. Moreover, improving the ability of viruses to selectively kill tumor cells to reduce damage to normal cells is one of the most important problems. Meanwhile, the immune clearance and tolerance of viruses are also important factors restricting the development of oncolytic virotherapy. Currently, many studies have demonstrated the potential of oncolytic virotherapy in the treatment of canine cancer. For example, one study found that treatment of osteosarcoma using an oncolytic virus can significantly inhibit tumor growth and prolong the survival of dogs. In addition, some studies reported the good effects of the oncolytic virus in the treatment of canine breast cancer, liver cancer, and brain tumors [25, 26]. The results show that the application of oncolytic virus therapy in canine cancer therapy is promising but still faces some challenges and limitations. Future studies will further refine and advance the effects of oncolytic virotherapy in clinical applications.

4. Checkpoint inhibitors

Immune checkpoint inhibitor therapy is a novel tumor immunotherapy method that activates the immune system by regulating the patient's own immune response to inhibit tumor growth and spread. The principle of this therapy is mainly based on the discovery of immune checkpoint molecules and the research results on immune tolerance. Immune checkpoint molecules are proteins on the cell surface that play an important role in regulating the activity of the immune system. Common immune checkpoint molecules are CTLA-4, PD-1, and PD-L1. Under normal circumstances, immune checkpoint molecules inhibit the activity of T cells and avoid excessive immune responses. However, in some tumor patients, tumor cells inhibit the function of T cells by overexpressing or over activating immune checkpoint molecules, thus evading the attack of the immune system. The central mechanism of immune checkpoint therapy is the reactivation of T cell function and killing ability by targeting these inhibitory signaling pathways. Among these, anti-CTLA-4 and anti-PD-1/PD-L1 antibodies are the two most commonly used immune checkpoint therapies. Anti-CTLA-4 antibody can inhibit the binding of CTLA-4 and its ligand and block its effect on T cell activity; anti-PD-1/PD-L1 antibody can block the binding of PD-1 and PD-L1 and restore the ability of T cells to attack tumors [27-30]. Immune checkpoint inhibition therapy may also have anti-tumor effects on canine cancers through mechanisms such as enhancing the killing ability of immune cells, promoting tumor cell apoptosis, and inhibiting tumor angiogenesis. Therefore, further studies investigating the mechanisms and response predictive markers of immune checkpoint therapy, as well as finding more effective combination treatment strategies, will be the focus of future research. This therapy did not achieve the desired therapeutic effect in a subset of patients, which may be related to the immune escape mechanisms in the tumor microenvironment. Meanwhile, since the research on canine cancer treatment is still in its infancy, further studies and clinical trials are needed to verify its efficacy and safety. Immune checkpoint therapies have achieved remarkable clinical results, especially in multiple tumor types such as malignant melanoma, non-small cell lung cancer, and breast cancer. There have been several preliminary studies of immune checkpoint suppression therapy in the treatment of canine cancer. Among them, an important study found that the application of PD-1 inhibitors to tumors significantly prolonged the survival of affected dogs with no obvious toxic side effects. This finding provides an important basis for the use of immune checkpoint suppression therapy in canine cancer therapy [31]. The results show that immune checkpoint inhibition therapy as a novel tumor treatment strategy has achieved remarkable success in human cancer therapy. However, its application in canine cancer treatment still needs further research and exploration [32-36].

5. Summary

Immunotherapy is an emerging treatment for canine cancers, and it has progressed significantly in recent years. The rationale for immunotherapy is to activate the immune system in dogs by enabling it to recognize and attack cancer cells. In the future, the development trend of immunotherapy in the treatment of canine cancer will be mainly reflected in the following aspects. First, individualized therapy will become an important direction for immunotherapy. Secondly, the application of multimodal immunotherapies will be widely promoted. For example, the combination of tumor vaccines and immune checkpoint inhibitors can promote the activation of the immune system and suppress the growth of cancer cells. Moreover, the development of gene-editing technology will provide more possibilities for immunotherapies. Through gene editing technology, immune cells in dogs can be modified to have stronger anti-cancer abilities. For example, the CRISPR-Cas 9 technology can be used to modify the genes of immune cells to better identify and attack cancer cells. In addition to conventional adoptive T cell therapy, immune checkpoint inhibitor therapy, and oncolytic virus therapy, several innovative approaches have emerged, such as gene editing techniques, photodynamic therapy, and nanotechnology. They offer new hope for canine cancer treatment.

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