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Canine Transmissible Venereal Tumor: Treatment Review and Updates

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ABSTRACT

Summary and Purpose: The increased resistant cases for treatment of canine transmissible venereal tumor (CTVT) have resulted in the emergence of several new alternatives. The current and most common therapeutic uses for the treatment of CTVT were reviewed and discussed in this article. Several new therapies, both clinically tested and currently in clinical trials, were also discussed. In addition, therapies, including the agents that were not effective for treating CTVT also being presented for future consideration in relation to the treatment usage.
Conclusion: New treatments for canine transmissible tumors are likely promising, especially for the cases that have developed resistance to certain treatments although these agents and/or therapies need to be more clarified in future studies. Nevertheless, the agents or thrapies that are not effective in treating CTVT are not expected to be used in treating the cases of CTVT.

Keywords
Canine; transmissible venereal tumor; present treatment, therapy

Introduction

Canine transmissible venereal tumor (CTVT) or known as venereal sarcoma, infectious sarcoma, venereal granuloma, or Sticker's tumor is a reticuloendothelial tumor in dogs (Martins *et al.*, 2005). This tumor has unique pathogenesis compared to other neoplasms, because its growth is not spontaneous but is transmitted through coitus, licking, and/or sniffing (Faccini *et al.*, 2019). Although the transmission was transmitted, no infectious particles, either bacteria or viruses, were found in the tumor cells (Ibrahim and Porter, 2012). This disease is at least endemic in about 90 countries around the world (Strakova and Murchison, 2014).

CTVT is divided into two types, i.e. genital and extragenital CTVT. Genital CTVT affects the genital area of dogs. In males, it generally affects the caudal aspect of the penis, and often the prepuce area, resulting in complications for example phimosis or paraphimosis. In female dogs, the lesions are common in the posterior vaginal area, particularly at the vestibulovaginal junction (Milo and Snead, 2014). Because of its deep location, it is sometimes not visible until it is massive (Kabusu *et al.*, 2010). The incidence of extragenital tumor cases is related to the characteristics of the tumor transmission that can be transmitted through licking and sniffing (Martins *et al.*, 2005; Murgia *et al.*, 2006). Even so, there are several reports of extragenital CTVT, such as tumors in the eyes, oral area, and skin with many treatment options provided.

Various treatments for CTVT cases are currently available, such as surgery, chemotherapy, and radiotherapy. The treatment modality that is often used is vincristine sulfate chemotherapy because it has been clinically proven to be efficient and has less serious risks/side effects. However, recently, resistance to this therapy is often found, therefore other alternatives are needed. Several alternatives are now available, some of which have been clinically tested and some are still in the testing phase. This review will discuss the latest developments of CTVT therapy.

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Current Agents and Treatment Options

Currently, there are several types of treatments for cases of TVT in dogs. Some of these treatments have been clinically tested, whereas some of them are still in the clinical trials for their effectiveness. Each treatment method has advantages and disadvantages, and the choice of the therapy must be taken into account based on the condition of the patient with TVT cases and the accessibility of available therapies.

Surgery

Surgical removal of the tumor in cases without metastases has a high successful rate. However, this action cannot be performed if the case of TVT is accompanied by metastases. The surgery is effective if the TVT case is in stage I, the tumor nodule is small, the site is easily accessible, and is non-invasive. TVT excision surgical methods can be performed conventionally, electric cautery, and cryosurgery (Arias *et al.*, 2016; Martins *et al.*, 2005). Conventional surgical methods are not a good approach because they are impractical in some areas of the body due to the anatomical location of the tumor which is difficult to reach, and the risk of recurrence after surgery (Das and Das, 2000). It is estimated that 50-68% of recurrences occur due to tumor cell transplantation in surgical wounds during conventional surgery (Ganguly *et al.*, 2013). Therefore, the surgery is usually combined with other therapies (Dameski *et al.*, 2019), for example using vincristine sulfate chemotherapy to completely clear the tumor cells (Takariyanti *et al.*, 2021). Postoperative recurrence is usually due to the invasive nature of CTVT. Tumor transplantation in surgical scars can occur due to exposure or contamination of gloves or surgical instruments (Oduye *et al.*, 1973; Martins *et al.*, 2005; Milo *et al.*, 2014).

Chemotherapy

One of the recommended treatment options for cases of TVT is chemotherapy. Several common chemotherapeutic agents, such as: vincristine sulfate, doxorubicin, cyclophosphamide, vinblastine, and methotrexate. And according to recent reports, lomustine can also be used as a TVT therapy. These drugs are used alone or as a combination therapy. Amber *et al.* (1990) stated that chemotherapy is better used than surgery in the patients who are in poor condition because it does not put the dog at risk of the effects of general anesthesia.

Vincristine Sulfate

Vincristine sulfate is generally the most effective chemotherapy for the treatment of TVT in dogs. This drug is the first choice in the treatment of TVT (Filho *et al.*, 2020). Vincristine sulfate is used because of its high effectiveness (estimated to remove tumors with a 90% success rate), relatively affordable price, and mild toxicity (Woods, 2020). The mechanism of action of vincristine sulfate is to stop cell division/mitosis at the metaphase stage (Said *et al.*, 2011). Vincristine sulfate chemotherapy is administered intravenously with saline or isotonic solutions (Küçükbekir *et al.*, 2021). The dose given is 0.5-0.7 mg/m^2 BSA (if converted based on the CDER (2005) in the form of mg/kg BW, then the dose given is 0.025-0.035 mg/kg BW) once a week, given two to six weeks until symptoms disappear (De

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Lorimier and Fan, 2007; Takariyanti *et al.*, 2021). Common side effects that may be caused after chemotherapy are neurotoxicity, paresthesia, and constipation. In male dogs, the side effect that may arise is a decrease in semen quality, but it will return to normal within 15 days after the last dose (Gobello and Corrada, 2002). If accidentally exposed topically, vincristine sulfate can cause significant skin irritation and even necrosis. In addition to the treatment of TVT, vincristine sulfate is used to treat lymphoma, sarcoma, and immune-mediated thrombocytopenia (Nak *et al.*, 2005). There are several cases of TVT resistance to vincristine sulfate therapy, this is related to the overexpression of a protein molecule called P-glycoprotein from the plasma membrane. This molecule is found in various tissues, such as: the spinal cord, peripheral blood, lungs, brain, colon, liver, and kidneys. Tumors expressing high amounts of P-glycoprotein tend to develop resistance to vincristine sulfate chemotherapy (Gaspar *et al.*, 2010). To overcome this, Andrade *et al.* (2009) combined vincristine sulfate with ivermectin. This antiparasitic drug proved to be efficient in minimizing resistance to vincristine sulfate, because ivermectin acts as a substrate for P-glycoprotein, thereby minimizing the expression of this protein. In addition to this combination, there are several other combinations such as combining with L-asparaginase. L-asparaginase is a chemotherapeutic agent that is widely used to treat canine leukemia and lymphoma. Sudjaidee *et al.* (2011) combined vincristine sulfate with L-asparginase with a dose of 10,000 IU/m^2 BSA. The results show a good response and with side effects that tend to be mild.

Doxorubicin

Doxorubicin is a chemotherapeutic agent that belongs to the class of tumor antibiotics. In addition to treating CTVT, doxorubicin is widely used to treat several carcinomas such as lymphoma, osteosarcoma, hemangiosarcoma, and thyroid carcinoma (Chu *et al.*, 2001). The first report in using the doxorubicin as an alternative therapy to vincristine sulfate was reported by Calvert *et al.* (1982) in which case dogs developed therapeutic resistance to vincristine sulfate. Calvert *et al.* (1982) also reported doxorubicin at a dose of 30 mg/m^2 BSA (1.5 mg/kg BW) intravenously to completely cure CTVT. However, another retrospective study conducted by Rogers *et al.* (1998) who used the same dose and found the tumor reappeared after two months. The cumulative dose of doxorubicin has a cardiotoxic effect, which is manifested by a decrease in systolic function accompanied by arrhythmias (Gustafson and Bailey, 2020). However, there are also several reports the success of therapy using doxorubicin in cases of resistance to vincristine sulfate. Cizmeci *et al.* (2012) and Chandrasekar *et al.* (2018) have reported that their therapy was successful, without tumor recurrence and without any side effects that endanger the patients. Doxorubicin should be considered if the patient is in good condition and does not have a heart defect that is resistant to vincristine sulfate.

Cyclophosphamide

Cyclophosphamide, also known as cytophosphane, is an alkylating agent. In the past, chemotherapy protocols for CTVT were initially combined with vincristine, cyclophosphamide, and methotrexate. Then, Amber *et al.* (1990) conducted a clinical investigation to test the effectiveness of these agents when used alone. The dose of cyclophosphamide 50 mg/m^2 BSA (2.5 mg/kg BW) given orally or intravenously when used as a single agent seems to give a partial response and is less effective.

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Methotrexate

As with cyclophosphamide, methotrexate is not effective and does not even have an effect on tumor regression when a single agent is used. Amber *et al.* (1990) reported that methotrexate at a dose of 2.5 mg/m^2 BSA (0.125 mg/kg BW) had no therapeutic effect at all, even partial effect.

Vinblastine

Vinblastine is a *vinca* alkaloid (Heijden *et al.*, 2004) and is a chemical substance analogous to vincristine (Sears and Boger, 2015). Vinblastine sulfate has similar effectiveness to vincristine sulfate. At a dose of 2.5 mg/m^2 BSA (0.125 mg/kg BW), vinblastine was able to eliminate the tumor. Due to its similar effectiveness, vincristine sulfate tends to be used because it is much cheaper than vinblastine. However, the side effects are similar to vincristine sulfate, i.e.: loss of appetite, mild diarrhea, and mild haematological changes (Ramadinha *et al.*, 2016).

Cisplatin

Cisplatin has been used successfully in the treatment of genital organ tumors except for the case of CTVT. Cizmeci *et al.* (2012) investigated the clinical effect of cisplatin because they thought that cisplatin might have had a therapeutic effect on CTVT. Based on reason that CTVT is a tumor in the genital organs. The study eventually found that cisplatin at a dose of 70 mg/m^2 BSA (3.5 mg/kg BW) was ineffective in treating CTVT. A study conducted by Cizmeci *et al.* (2012) who used dogs in the clinical trial of cisplatin. The dogs experienced death due to the side effects, including nephrotoxicity which was clinically manifested in anorexia, vomiting, tachycardia, tremor, and depression.

Lomustine

Lomustine is an alkylating nitrosourea compound used as chemotherapy. This drug is fat-soluble, so it can easily cross the blood-brain barrier. In the veterinary world, lomustine is commonly used to treat mast cell tumors in dogs (Weiss *et al.*, 2010), and may be able to treat brain tumors in dogs, because as previously described this drug can cross the blood-brain barrier. The use of lomustine as a TVT treatment in dogs was first reported by Barboza *et al.* (2021). The case dog in the report developed resistance to vincristine sulfate. One alternative to chemotherapy other than vincristine sulfate is doxorubicin. Before being given doxorubicin, the dog was examined using echocardiography. After an echocardiographic examination, the dog did not allow therapy with doxorubicin. As previously mentioned, doxorubicin has a side effect of inducing cardiotoxicity, so that in dogs with heart disease or disorders, chemotherapy with this agent cannot be done (Gustafson and Bailey, 2020).

Barboza *et al.* (2021) then performed therapy using lomustine which had not previously been reported. The dose given is 60 mg/m^2 BSA (3 mg/kg BW), given orally three times gradually once a week. The results of the therapy have proven to be effective without any side effects. The results of the complete blood count (CBC) and blood biochemistry did not show any abnormalities after using lomustine therapy. After 24 months of post-therapy follow-up,

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TVT did not reappear. Lomustine should be considered if the dog is resistant to vincristine sulfate and it is not possible to take doxorubicin.

Radiotherapy

Wong and K'Ang (1932) first reported that CTVT is very sensitive to irradiation. Small doses can be used for this disease. Radiotherapy is indeed effective in treating CTVT because it can completely clean tumor cells. However, radiotherapy requires special equipment and well-trained personnel to use the equipment. As a result, the costs required become expensive (Martins *et al.*, 2005; Milo *et al.*, 2014). The recommended dose ranges from 1500 to 2500 rads, divided into several sessions of 400-500 rads in a period of 1-2 weeks, the cure rate is close to 100% without leaving scars. In addition, another drawback is the mandatory use of general anesthesia in this procedure. Even so, severe cases with metastases cannot carry out radiotherapy protocols.

Oncolytic viruses

Oncolytic viruses are viruses that can selectively replicate in cancer cells and kill them, even stopping the uncontrolled growth cycle of cancer. CTVT therapy using oncolytic viruses that have been reported is the use of non-structural protein 1 (ns1) gene from Canine Parvovirus-2 (CPV-2) and viral protein 3 (vp3) gene from chicken anemia. Preclinical studies have been conducted on cancer cells line by Saxena *et al.* (2015) and in animal models of mice (Santra *et al.*, 2014).

The first study and clinical application in dogs with CTVT were conducted by Bhat *et al.* (2017). As a result, the two genes of the virus can partially induce oncolysis in dogs. Bhat *et al.* (2017) intratumorally injected 100 g of the ns1 gene, vp3, and a combination of ns1 and vp3. Dogs with CTVT treated with these genes showed a decrease in tumor mass from mild to moderate, black in color, and ulcerated. During three weeks post-therapy, both ns1 and vp3 affected the nuclei of neoplastic cells causing karyorrhexis and karyolysis, leading to a decrease in the number of tumor cells accompanied by lymphoid cell-infiltrated fibrosis. In addition to the decreased number of tumor cells, the mitotic index was also suppressed and increased apoptotic activity based on the TUNEL assay. Among the three treatments, the ns1 gene showed the best oncolytic effect. However, the results obtained are less convincing and its effectiveness is still doubtful.

Conclusion

New treatments for canine transmissible venereal tumor (CTVT) are promising, especially for the related cases that have developed resistance to certain treatments, for example lomustine can be used in the CTVT-vincristine sulfate resistant case Some of them have been clinically tested and practitioners who are encountering cases of CTVT resistance can apply them for the alternatives. Agents that have not been clinically tested are expected to need to be clarified and investigated in further studies in the future. Meanwhile, the agents that are not effective in treating CTVT are not expected to be used in treating cases of CTVT, i.e. cyclophosphamide, methotrexate and cisplatin.

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Authors Contribution

PSS devised this review, the main conceptual ideas, and write the manuscript. IMK helped supervise and critically revised the manuscript. Both PSS and IMK authors contributed to the final version of the manuscript. All authors are equally contributed to this manuscript.

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