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KNOWLEDGE SUMMARY

Keywords: CANINE; COMBINATION THERAPY; IVERMECTIN; P-GP; TVT; VINICRISTINE

Efficacy of vincristine-ivermectin combination therapy in the treatment of canine transmissible venereal tumour (CTVT)

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PICO question

In dogs diagnosed with canine transmissible venereal tumour (CTVT), does treatment with vincristine combined with ivermectin, compared to treatment with vincristine alone, lead to improved clinical outcomes?

Clinical bottom line

Category of research	Treatment.
Number and type of study designs reviewed	Two randomised controlled trials.
Strength of evidence	Weak.
Outcomes reported	The studies collectively indicate that the combination of vincristine and ivermectin may be an effective and well-tolerated treatment for CTVT, with potential advantages over vincristine alone. One study demonstrated a statistically significant reduction in the number of treatment sessions for tumour remission, although methodological limitations and the absence of long-term follow-up limit the evidence. The other study observed comparable treatment efficacy across groups and a trend toward improved tolerability, despite the presence of cytomorphologically resistant types in the combination group; however, these differences were not statistically significant.
Conclusion	Ivermectin, a synthetic avermectin, may augment the action of vincristine when used for the treatment of CTVT. This may reduce the duration of therapy, lessen side effects, minimise recurrence and in turn reduce the animal's suffering. Overall, the evidence to support this is assessed as weak.

How to apply this evidence in practice

The application of evidence into practice should take into account multiple factors, not limited to: individual clinical expertise, patient's circumstances and owners' values, country, location or clinic where you work, the individual case in front of you, the availability of therapies and resources.

Knowledge Summaries are a resource to help reinforce or inform decision-making. They do not override the responsibility or judgement of the practitioner to do what is best for the animal in their care.

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Clinical scenario

An owner presents her pet dog, with blood oozing from the vulva, which also shows a visible mass. There is a history of mating approximately a month back. Clinical examination and cytological evaluation confirm the condition to be canine transmissible venereal tumour (CTVT). The owner prefers a non-surgical treatment option. You have heard of medical management of CTVT involving vincristine-ivermectin combination therapy. To justify the addition of ivermectin alongside vincristine, you seek appropriate scientific evidence supporting its role in the therapy.

The evidence

The literature search for comparing the efficacy of vincristine-ivermectin combination over vincristine therapy alone for CTVT in dogs yielded two randomised control studies (Bulhosa et al., 2020; Lapa et al., 2012). Both compared the vincristine-ivermectin combination therapy with vincristine therapy in randomly assigned groups of dogs diagnosed with CTVT. Bulhosa et al. (2020) found tumour remission of combination treatment to be comparable with vincristine alone treatment, despite finding a higher proportion of resistant tumour types in the combination treatment group. A trend towards fewer adverse reactions and faster remission was also observed, although this was statistically non-significant. Lapa et al. (2012) reported fewer chemotherapy sessions were required with the combination treatment. The overall strength of evidence is weak.

Summary of the evidence

Bulhosa et al. (2020)

Vincristine and ivermectin combination chemotherapy in dogs with natural transmissible venereal tumour of different cyto-morphological patterns: A prospective outcome evaluation

Aim: To determine the frequency of CTVT cyto-morphologies, and compare the treatment efficacy and adverse reactions to vincristine alone compared with a combination vincristine and ivermectin.

Population	Dogs diagnosed with canine transmissible venereal tumour (CTVT) at the Teaching Hospital of Veterinary Medicine of the Federal University of Bahia, in Salvador, Brazil, excluding those with comorbidities.
Sample size	20 dogs.
Intervention details	• The sample population were randomly selected and divided into two treatment groups. • Vincristine alone (G-Vin) group (n = 10): given vincristine weekly at a dose rate of 0.5 mg/m^2 of body surface area diluted in 10 mL 0.9% sodium chloride until the tumour regressed. • Ivermectin-vincristine (G-Iv/Vin) group (n = 10): given ivermectin 1% at 0.5 mg/kg 24 hours before administering vincristine at a dose of 0.5 mg/m^2 at 2-week intervals until tumour remission.
Study design	Randomised controlled trial.
Outcome studied	Clinical examination, physical examination, haemogram, and tumour cytology evaluation, before each weekly chemotherapy session to assess the health status and extent of tumour regression.
Main findings (relevant to PICO question)	• Despite the high frequency of highly resistant plasmacytic and mixed CTVT cell types and poor clinical status of patients in the G-Iv/Vin group, the same effectiveness and fewer adverse reactions were observed compared to the G-Vin group.

- In the G-Iv/Vin group tumour remission occurred a week faster than that of the G-Vin group, but this was not found to be statistically significant.
- While the dogs of the G-Vin group had a decrease in mean leucocyte count, neutrophils, and monocytes, in the G-Iv/Vin group, variables were within the reference range.
- A dog of G-Iv/Vin group with poor clinical status and metastases showed weight loss following the first chemotherapy session and improvement and recovery in subsequent sessions.

Limitations

- Small sample size.
- Method of randomisation not mentioned and hence the chance of bias.
- Initial diagnosis solely based on fine needle aspiration cytology (FNAC).
- The randomisation resulted in imbalanced groups, with the G-Iv/Vin group having dogs with highly resistant tumour cells and poor clinical status as determined by a structured clinical severity scoring system.
- No molecular analysis: lacks P-glycoprotein (P-gp) or MDR1 gene expression data to confirm ivermectin's role in overcoming drug resistance.

Lapa et al. (2012)

Histopathological and cytological analysis of transmissible venereal tumour in dogs after two treatment protocols

Aim: To compare the effectiveness of standard vincristine treatment alone with combined vincristine and ivermectin treatment for CTVT, by assessing number of applications, histopathological findings and cytological changes.

Population

Dogs diagnosed with canine venereal transmissible tumour (CTVT) between August 2007 to March 2010.

Sample size

50 dogs.

Intervention details

- Dogs randomly grouped into vincristine group (VG) and vincristine-ivermectin group (VIG).
- Vincristine group (VG): 25 dogs consisting of 11 males and 14 females of age 4.0 ± 2.4 years; weight: 13.7 ± 6.2 kg.
- Vincristine with ivermectin group (VIG): 25 dogs consisting of seven males and 18 females of age 4.9 ± 2.2 years; weight: 11.8 ± 7.3 kg.
- VG treated with intravenous administration (IV) of vincristine sulphate (1 mg/mL) at a dose of 0.5 mg/m^2 once a week.
- VIG treated with (IV) of vincristine sulphate (1 mg/mL) at a dose of 0.5 mg/m^2 once a week, followed by ivermectin (1.0 g/100 mL) at a dose of 400 µL/kg subcutaneously once a week.

Study design

Randomised controlled trial.

Outcome studied

Physical examination, white and red blood cell count, cytology, and biopsy of tumour weekly before administration of anti-neoplastic treatment.

Main findings (relevant to PICO question)	The number of treatments required to effect recovery in VIG group (3.2 ± 1.8) was significantly less than that of VG group (5.5 ± 1.8).
Limitations	• No molecular analysis: lacks P-glycoprotein (P-gp) or MDR1 gene expression data to confirm ivermectin's role in overcoming drug resistance. • No untreated control group lacks a placebo or natural progression comparison for CTVT. • Limited sample size: 50 dogs may not be representative of the broader canine population. • Tumour staging unclear: tumour, node and metastasis (TNM) classification to assess treatment response based on tumour burden. • Short follow-up: lacks long-term monitoring for recurrence. • Side effects underreported: no detailed evaluation of adverse reactions to vincristine-ivermectin therapy. • Incomplete tumour regression analysis: lacks specific findings on histopathological, apoptotic, or necrotic changes. • Environmental factors unexplored: assessment of climate, breed distribution, or regional CTVT variations.

Appraisal, application and reflection

Canine transmissible venereal tumour (CTVT) is a horizontally transmitted round-cell tumour spread through coitus, sniffing, and licking, producing genital and extragenital lesions (Purohit, 2009). Chemotherapy remains the mainstay of treatment, with vincristine sulphate being the most widely used agent due to its efficacy, affordability, and relatively mild side effects (Purohit, 2009). It acts by arresting cells in metaphase and is administered weekly at 0.5–0.7 mg/m² or 0.025–0.035 mg/kg until remission. Reported adverse effects include neurotoxicity, constipation, paraesthesia, and reduced semen quality. Other chemotherapeutic options include doxorubicin (effective but cardiotoxic), cisplatin (nephrotoxic), cyclophosphamide, methotrexate (ineffective for CTVT), and lomustine (effective but with limited clinical data) (Sewoyo & Kardena, 2022).

Vincristine resistance poses a major challenge and arises from altered gene expression, enhanced detoxification, increased DNA repair, and overexpression of efflux pumps such as P-glycoprotein (P-gp) (Abeka, 2019). Tumours with high P-gp levels show poor response to vincristine (Gaspar et al., 2010).

P-glycoprotein (P-gp) mediates drug efflux and contributes significantly to multidrug resistance. Several P-gp modulators – including cyclosporin derivatives, verapamil, cyclosporin A, and ivermectin – have been identified (Didier & Loor, 1996). Vincristine is a P-gp substrate, and combining it with ivermectin has shown improved early remission in CTVT. Didier & Loor (1996) demonstrated strong in vitro P-gp inhibition and reversal of drug resistance by ivermectin, while Jiang et al. (2019) revealed in vivo that ivermectin restores vincristine sensitivity by suppressing the EGFR/ERK/Akt/NF-κB pathway. Avermectins have also demonstrated antitumour and resistance-reversing effects in both in vivo (Drinyaev et al., 2004) and in vitro (Korystov et al., 2004) studies.

Bulhosa et al. (2020) evaluated the use of ivermectin in combination with vincristine for the treatment of CTVT. In this study, even though the vincristine-ivermectin group included a higher proportion of dogs with highly resistant cytomorphological tumour types, tumour remission was comparable to that observed in the vincristine-alone group. While the vincristine-ivermectin group showed a trend toward fewer adverse reactions and slightly faster tumour remission, these differences were not statistically significant. Nonetheless, these findings suggest potential clinical relevance, indicating that ivermectin may help maintain treatment tolerability and support therapeutic response, particularly in dogs with more aggressive or resistant tumours. Similarly,

Lapa et al. (2012) reported that the vincristine–ivermectin combination could reduce the number of chemotherapy sessions required for tumour remission. Together, these studies indicate that incorporating ivermectin into standard vincristine protocols may have potential benefits in the clinical management of CTVT, although further research with larger sample sizes and standardised treatment regimens is needed to confirm these effects.

The studies on CTVT treatment had several limitations that affect the generalisability and robustness of their findings. Both studies had small sample sizes (20–50 dogs) limiting statistical power. Follow-up durations were also short, typically lasting only a few weeks, without long-term evaluation of recurrence or resistance, which is crucial for assessing sustained remission. One study had unequal disease severity at baseline, with more severe cases in the vincristine-ivermectin group, potentially affecting treatment outcomes. Furthermore, side effects were not comprehensively assessed, with only mild leucopenia, neutropenia, or anorexia reported, while other potential toxicities (e.g., gastrointestinal, neurological, or hepatotoxic effects) were not thoroughly analysed. Despite suggestions that ivermectin may counteract vincristine resistance, no molecular studies confirmed this by analysing Multi Drug Resistance 1/P-glycoprotein (MDR1/P-gp) expression. While some studies characterised tumour subtypes cytologically, they did not systematically analyse the correlation between tumour type and treatment response, and tumour, node and metastasis (TNM) staging was inconsistently considered. Case selection and treatment allocation were not always randomised, increasing the risk of selection bias, and drug administration techniques (e.g., vincristine infusion rate, ivermectin injection site) were not standardised, potentially affecting results. Lastly, the influence of geographical, environmental, and breed-related factors on treatment response was not explored, despite potential differences in susceptibility or drug metabolism. Addressing these limitations in future studies through larger sample sizes, randomised controlled trials, long-term follow-ups, and molecular analyses would provide stronger evidence for optimal CTVT treatment strategies.

Ivermectin, with its reported anti-tumour properties and potential to modulate chemoresistance via P-gp inhibition, may serve as an adjunct to vincristine for the treatment of canine transmissible venereal tumour. Although some studies suggest trends toward fewer treatment sessions and improved tolerability, evidence regarding side effects, treatment duration, and long-term outcomes remains limited and inconclusive.

Methodology

Search strategy	
Databases searched and dates covered	CAB Abstracts via Web of Science (1973–2025) PubMed via NCBI website (1995–2025) Google Scholar (search performed 20 Feb 2025)
Search strategy	CAB Abstracts: 1. (Vincristine or anti-tumor or anti-tumour or combination chemotherapy) 2. (ivermectin or avermectins) 3. (canine transmissible venereal tumour or TVT) 4. 1 and 2 and 3 PubMed: (Vincristine or chemotherapy) AND (ivermectin or avermectins) AND (canine transmissible venereal tumour or CTVT) (combination therapy) AND (canine transmissible venereal tumour OR CTVT). Google Scholar: Vincristine ivermectin combination therapy for canine transmissible venereal tumour
Dates searches performed	20 February 2025

Exclusion / Inclusion criteria	
Exclusion	• Studies not relevant to the PICO. • Studies not written in English. • Review papers. • Conference proceedings. • Case reports. • Thesis. • Non-comparative study.
Inclusion	• Primary research paper relevant to PICO. • Studies demonstrating the efficacy of vincristine-ivermectin combination therapy on CTVT.

Search outcome					
Database	Number of results	Excluded — not relevant to the PICO	Excluded — thesis, case reports, conference papers, review articles, other language, document not available	Excluded — duplicates	Total relevant papers
CAB Abstracts	1295	1177	118	0	0
PubMed	21	8	12	0	1
Google Scholar	112	28	82	1	1
Total relevant papers when duplicates removed					2

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Conflict of Interest
The author declares no conflicts of interest.

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