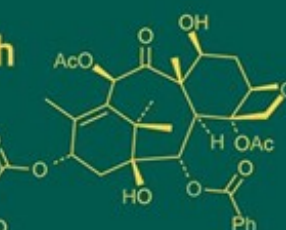


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Chemotherapy in bovine oncology: Principles, applications and recent advances

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ABSTRACT

Neoplastic diseases in cattle and buffaloes can adversely affect animal health, productivity and welfare, necessitating effective diagnostic and therapeutic strategies. Chemotherapy represents an important therapeutic option for selected neoplasms and may be used as a primary treatment, an adjunct to surgery, or as part of multimodal cancer management. This review summarises the principles, applications and recent advances in chemotherapy for bovine neoplasia. The fundamental concepts of antineoplastic chemotherapy, including conventional maximum tolerated dose chemotherapy, metronomic chemotherapy, and targeted therapy, are discussed, along with treatment objectives, drug selection, dosing principles, and mechanisms of therapeutic action. Particular emphasis is placed on the chemotherapeutic management of important bovine tumours, including papillomatosis, squamous cell carcinoma, oral tumours and lymphosarcoma. Reported therapeutic approaches include systemic and intralesional administration of agents such as vincristine, mitomycin C, cisplatin and L-asparaginase, as well as immunotherapeutic and adjunctive treatment modalities. The review also highlights the importance of appropriate patient selection, tumour characteristics, treatment response and adverse-effect monitoring in determining therapeutic outcomes. Safe handling, administration and disposal of cytotoxic drugs are discussed because of the potential occupational hazards associated with these agents. Recent developments, including immunotherapy, molecularly targeted approaches and RNA interference-based therapies, indicate emerging opportunities for more selective and potentially personalised treatment of bovine neoplasia. Overall, understanding tumour biology, available chemotherapeutic protocols, and treatment-specific considerations is essential for the rational application of chemotherapy in bovine oncology and for improving therapeutic outcomes while maintaining animal welfare.

Keywords: Bovine oncology, Chemotherapy, Bovine neoplasia, Papillomatosis, Squamous cell carcinoma, Oral tumours, Lymphosarcoma, Targeted therapy, Immunotherapy

Introduction

The contemporary use of pharmacological treatments for cancer started in the mid-1940s, when Alfred Gilman and Louis Goodman demonstrated the effectiveness of nitrogen mustard in mice with tumours, and these findings were promptly applied and confirmed in human patients (Vail *et al.*, 2019) [1]. Chemotherapy is defined as the administration of pharmacological agents to eliminate or inhibit the proliferation of viruses and foreign cells, such as bacteria or fungi, within the body. Although cancer cells are derived from the host's own tissues, they are recognised as "foreign" in this context (Riviere and Papich, 2018).

These foundational discoveries in cancer pharmacotherapy have directly shaped veterinary oncology practice. Building on these advances, chemotherapy modalities now serve as a cornerstone in the management of many cancers encountered in companion animals, livestock, and exotic species. While veterinary oncology employs many of the same chemotherapeutic agents used in human medicine, protocols, dosing, and objectives are carefully adapted to address the unique physiological needs and welfare considerations of animal patients. In order to provide a clear and systematic evaluation of chemotherapy in veterinary oncology, this discussion will begin by defining key technical terms related to chemotherapeutic agents, then will compare and contrast major therapeutic approaches, and finally, will explore specific clinical applications and outcomes in animal patients.

When discussing chemotherapeutic agents, several technical terms are frequently encountered, and a brief comparative overview of these approaches clarifies their distinctions before examining the field in detail. 'Conventional chemotherapy' utilises cytotoxic drugs at the highest tolerated cycles to eliminate rapidly dividing cells, but its lack of selectivity can result in collateral effects on normal tissues. In contrast, 'metronomic chemotherapy' administers low doses frequently and continuously, focusing primarily on disrupting tumour angiogenesis and potentially reducing toxicity and resistance. 'Targeted chemotherapy using tyrosine kinase inhibitors (TKIs)' offers a more specific intervention by blocking tyrosine kinases essential for cancer cell growth and survival signaling. The choice among these strategies reflects a synthesis of therapeutic

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goals: maximizing tumour control, minimizing adverse effects, and aligning with the individual patient's clinical status and owner's resources.

Conventional chemotherapy

Conventional chemotherapy, often referred to as maximally tolerated dose (MTD) chemotherapy, involves administering chemotherapeutic agents at the highest recommended dosage, followed by a recovery phase for drug-sensitive cells, including those in the bone marrow and gastrointestinal tract. This approach aims to achieve the greatest possible reduction in tumour cells while typically carrying a lower risk of severe side effects. However, the intervals between treatment sessions can also permit tumour regrowth. Depending on the tumour type and disease stage, MTD chemotherapy may be used alone or as an adjunct to surgery or radiation therapy. In solid tumours, such as osteosarcoma, it is often used as adjuvant therapy after primary treatment to help prevent progression of occult micrometastatic disease (Biller *et al.*, 2016) [2]. A micrometastasis is defined as a lymph node metastasis larger than 0.2 mm and/or containing more than 200 cells but not exceeding 2.0 mm in size. In contrast, isolated tumour cells or clusters measuring less than 0.2 mm are referred to as ITCs (Zhang *et al.*, 2013) [3]. The primary objectives of conventional chemotherapy are to control tumour growth while maintaining or improving the patient's quality of life (Biller *et al.*, 2016) [2].

Metronomic chemotherapy

Metronomic chemotherapy is characterised by the continuous delivery of low doses of cytotoxic medications at regular and frequent intervals. Recent research suggests this approach may be as effective as traditional chemotherapy while causing lower toxicity and cost (Browder *et al.*, 2000; Emmenegger *et al.*, 2004) [4, 5]. Unlike maximum tolerated dose (MTD) chemotherapy, which targets rapidly dividing cancer cells, metronomic chemotherapy primarily targets tumour angiogenesis. The endothelial cells recruited to facilitate tumour growth are particularly sensitive to low, uninterrupted doses of chemotherapy agents (Kerbel *et al.*, 2004) [6]. Furthermore, the genetic stability of these endothelial cells makes them inherently less likely to develop drug resistance than cancer cells (Mancuso *et al.*, 2006) [7]. Consequently, metronomic chemotherapy tends to produce fewer adverse effects on non-endothelial cells, such as epithelial cells and leukocytes. Unlike conventional chemotherapy, which typically aims for a reduction in tumour size, the objective of metronomic

chemotherapy is often to stabilise the disease. Most veterinary oncologists consider metronomic chemotherapy for cases where conventional treatment has failed, or the pet owner has declined it (Biller *et al.*, 2016) [2].

Targeted chemotherapy using tyrosine kinase inhibitors

Tyrosine kinases are enzymes that activate proteins involved in signalling pathways that regulate normal cell growth and survival. Because many of these pathways are disrupted in cancer cells, tyrosine kinase inhibitors (TKIs) act as *anti-cancer* drugs that block signal transduction, thus preventing tumour growth (Biller *et al.*, 2016) [2]. Mutations in the c-kit gene, an RTK associated with mast cell differentiation and proliferation, occur in approximately 25% of canine mast cell tumours (Barber & Burgess, 2023). Currently, two oral TKIs have been approved for use in dogs with cancer: toceranib phosphate and masitinib mesylate (conditionally approved in the United States). These TKIs are indicated for specific grades and stages of mast cell disease (Biller *et al.*, 2016) [2]. Although these drugs target specific signalling pathways, they can also cause toxicity in rapidly dividing normal cells that rely on these pathways. Broader use of TKIs requires further investigation into critical questions, such as which tumour types are most likely to respond to TKIs and their optimal combination with conventional chemotherapy agents (Biller *et al.*, 2016) [2].

The potential of harnessing the immune system to combat cancer presents significant opportunities for treating aggressive malignancies, particularly for the prevention and management of metastatic disease. One notable advancement is the development of the first U.S. Department of Agriculture-licensed immunotherapeutic agent for veterinary oncology: the canine melanoma vaccine. This DNA vaccine is specifically indicated for dogs diagnosed with stage II or III oral melanoma, where local disease control has already been established. It operates by leveraging the immune response to human tyrosinase, an enzyme crucial in melanin synthesis. The formulation contains a human tyrosinase gene integrated into a bacterial plasmid and is delivered transdermally. The immune reactions elicited by xenogeneic tyrosinase can cross-react with tyrosinase overexpressed on canine melanoma cells. Preliminary studies indicate that dogs with advanced-stage oral malignant melanoma that received radiation or surgical treatment for the primary tumour, followed by vaccination, experienced improved survival outcomes.

Term	Definition
Cure	The complete eradication of all tumor cells from the body. This goal is often not achievable in most cases.
Palliation	The reduction of pain and improvement of a patient's function to enhance their quality of life, in situations where a cure is not possible. It's an increasingly recognized and acceptable therapeutic goal.
Therapeutic Index	The ratio of the toxic dose to the therapeutic dose of a drug. In the context of cytotoxic drugs for cancer, this is often considered an abstract concept.
Maximum Tolerated Dose (MTD)	The highest dose of a drug that can be given with a low chance of causing unacceptable or irreversible side effects. This value is determined through clinical experience and is the basis for most cancer drug dosing.
Biologically Effective Dose (BED)	A newer dosing concept for cancer drugs based on a measured biological response at a specific target. This is particularly relevant for molecularly targeted agents and signal transduction inhibitors but could also be applied to other drugs.
Dose Intensity (DI)	A measure of the drug dose given per unit of time. It's used to compare different dosing schedules to see if the total dose or the rate of administration affects the outcome or toxicity.
Therapeutic Gain	The improved tumor response achieved when combining two drugs or a drug with radiation, relative to any increase in toxicity to normal tissues. It is considered positive when the combined tumor effects are greater than the combined toxicity.
Primary Neoadjuvant Chemotherapy	The use of chemotherapy drugs before other treatments, most often surgery, to shrink the primary tumor, decrease its clinical stage (downstaging), and prevent the growth of micrometastases that may occur after surgery.
Adjuvant Chemotherapy	The use of chemotherapy drugs after the primary tumor has been surgically removed or controlled by radiation. Its purpose is to treat any remaining, hidden disease, such as residual tumor cells after incomplete excision or micrometastases.

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Term	Definition
Consolidation Therapy	Reintensification of therapy (used most commonly with hematopoietic cancers) after remission is attained to further reduce the likelihood of relapse.
Maintenance Therapy	Low-intensity therapy given over a protracted period of time after remission is attained.
Rescue or Salvage Therapy	The use of chemotherapy after a tumor fails to respond to a previous therapy or after tumor recurrence
Radio-sensitization	The enhancement of cytotoxicity when irradiation and chemotherapeutic agents are combined such that a therapeutic gain is obtained
Occult Disease	Disease that is not clinically detectable but is present; often the target of adjuvant chemotherapy.
Palliative Chemotherapy	Delivered to decrease clinical signs in the case of unresectable or disseminated disease that is associated with functional disturbances or pain. The outcome is based more on quality of life issues..
Mitotic Index (MI)	The proportion of cells in the process of mitosis within a tumor. (Reported by a pathologist as MI or as the number of mitoses per high-power field).
Growth Fraction (GF)	The proportion of proliferating cells within a tumor. (Cannot be quantified in a patient).
Doubling Time (DT)	The time it takes for a tumor to double in size. (Calculated using sequential measurements of tumor volume $[V = \frac{\pi}{6} \times (\text{mean diameter})^3]$ seen on imaging or determined by direct palpation).

Additionally, evidence from equine studies has shown either stabilisation or reduction in tumour size, alongside the emergence of *anti*-tyrosinase immunoreactivity. Furthermore, therapeutic autologous cancer vaccines utilise the patient's tumour to induce unique tumour-associated antigens. These vaccines are often administered alongside adjuvants to enhance the immune response and overcome tolerance to these antigens, aiming for immune-mediated destruction of cancer, especially in cases of microscopic metastatic disease (Barber & Burgess, 2023).

Basic principles of antineoplastic chemotherapy in animals

A combination of three or more drugs is commonly used to treat a given neoplasm. These chemotherapeutic agents are selected based on certain principles. Each drug should have a different mechanism of action, should have the desired action against the targeted tumour, and should not have overlapping toxicities. This helps to harness the antineoplastic effects of multiple drugs with maximum desired action and minimal side effects. It is conventional to name the designed protocol after the first letters of chemotherapeutic agents employed for treatment. Common examples of multi-agent protocols include CHOP (cyclophosphamide, doxorubicin [hydroxydaunorubicin], vincristine [Oncovin], and prednisone), which is frequently used for lymphoma in dogs, and COP (cyclophosphamide, vincristine [Oncovin], and prednisone), which is used as a less intensive alternative. For mast cell tumours, the VLP protocol (vinblastine, lomustine, prednisone) is sometimes chosen, while VAC (vincristine, actinomycin D, cyclophosphamide) may be used for osteosarcoma. Knowledge of these standard protocols aids selection based on tumour type and supports memorization. These multi-agent combinations delay or even prevent the development of drug-resistant clones, contributing to longer remissions and survival times than single-agent chemotherapeutic protocols. However, in certain cases, single-agent chemotherapeutic regimens are as effective as combination protocols; for example, in CTVT, vincristine, doxorubicin or carboplatin as single agents. Another principle worth mentioning is that chemotherapy is more effective in a relatively smaller tumour than in a larger one, even if the inherent sensitivity to the drug is the same in both cases. This is because the smaller tumour has a higher mitotic index (MI) and growth fraction (GF), resulting in a shorter doubling time (DT). In other words, more cells are actively dividing at any given moment in the smaller tumour. This is clearer in Fig. (Nelson *et al.*, 2019) [8].

Based on tumour growth dynamics, when a pulmonary metastatic nodule is visible on radiographs or detected sonographically, it contains more than 200 million cells and weighs less than 150 mg. In contrast, a 1-cm palpable nodule contains approximately 1 billion tumour cells (or 1 trillion) and weighs about 1 g (Nelson *et al.*, 2019) [8].

Chemotherapeutic drug dosing is based on body surface area and not on an animal's body weight. This is because physiological processes

affecting drug activity correlate better with body surface area than with body weight. However, there is an exception to body surface area dosing: in very small patients (weighing less than 10 kg), BSA-based dosing leads to a comparatively higher dose and consequent adverse effects, so body weight-based dosing may be chosen. Weight can be converted to surface area using this formula:

$$BSA (m^2) = \frac{(K \times \text{Weight in grams})^{2/3}}{10,000}$$

K is a species constant with a value of 10.0 and 10.1 for cats and dogs, respectively (Riviere and Papich, 2018).

For example, to calculate the body surface area of a 20 kg dog:

First, convert weight to grams:

$$20 \text{ kg} \times 1000 = 20,000 \text{ grams}$$

Apply the formula using *K* = 10.1 (for dogs):

$$BSA = \frac{(10.1 \times 20,000)^{2/3}}{10,000}$$

Calculate the value inside the parenthesis:

$$10.1 \times 20,000 = 202,000$$

Now, raise to the 2/3 power:

$$202,000^{2/3} \approx 3,457$$

Finally, divide by 10,000:

$$BSA \approx 3,457/10,000 = 0.346 \text{ m}^2$$

Therefore, the body surface area for this 20 kg dog is approximately 0.35 m².

Administration guidelines

These chemotherapeutic guidelines are for small animals, but because resources in large-animal practice in developing countries are limited, they are difficult to adapt; however, they are included here to support adaptation to evolving standards and ethics. A key element of the safety program is the availability of Safety Data Sheets (SDS, formerly called Material Safety Data Sheets [MSDS]). The updated Hazard Communication System requires Safety Data Sheets (SDS) to follow a standardised format that includes essential information for the safe management of chemical substances. This includes guidelines for handling materials, recommended personal protective equipment, spill-response procedures, first-aid protocols, and toxicological data

detailing exposure routes and associated symptoms. Gather information sheets for each antineoplastic agent used in the hospital into a binder and make them accessible for staff review. Only trained personnel should handle and administer chemotherapeutic reagents, and training should be well documented in staff personnel files and, in case of owners, in the patient's medical record.

PPE Recommendations for preparation, administration, spill and waste management, and inventory management

- Chemotherapy-rated (ASTM International [American Society for Testing and Materials]) double-gloving
- Long-sleeved coated impermeable gown with back closure
- Shoe coverings
- Shoe & hair coverings to maintain sterility (if needed)
- Eye shield/Face shield if potential for splashing/aerosolization
- Respirator (fitted)

Before administration, examine the HD for leakage while it is contained in the transport bag. Verify the patient's identification, drug name, and dosage. If the HD appears intact and the dose is correct, remove it from the transport bag. Place a plastic-backed absorbent pad under the administration area to absorb leaks and prevent drug contact with the patient's skin.

Two trained persons donning PPE kits are required to administer chemotherapy. To reduce personnel contamination, perform all work below eye level. Chemotherapeutics administered PO should not be broken or crushed, and capsules should not be opened; they should be given intact. Intralesional chemotherapy may pose a high environmental hazard and risk personnel contamination; therefore, extra measures may be needed to prevent contamination, such as cleaning the area afterwards and possibly covering it, depending on the amount of leakage. A full face shield is recommended. When administering injectable chemotherapy, place a catheter (the smallest gauge and shortest length that can accommodate therapy) with a single, successful insertion (a "clean stick") to prevent extravasation and ensure patient safety and personnel protection. Never use heparinised saline to irrigate lines or catheters because it can precipitate with certain chemotherapy agents and increases the risk of extravasation due to local bleeding. Whenever feasible, avoid an IV pump to minimise pressure on veins, reduce the likelihood of extravasation, and lower the chances of disconnection and spills. For non-HD administration, such as with monoclonal antibodies or bisphosphonates, a syringe or infusion pump is acceptable, especially for prolonged infusions like continuous rate infusions (CRI) of cytosine arabinoside and dacarbazine. After administering treatment, remove the IV catheter while keeping the lines and tubing intact. Remove the outer glove inside out, ensuring the IV catheter remains contained within it. Dispose of all administration materials appropriately, and follow decontamination procedures strictly. Wear gowns for no longer than three hours to prevent permeation, and discard them after each use or sooner if soiled.

Common Side Effects and Their Management

Chemotherapy in animals can lead to a variety of adverse effects, most commonly affecting tissues with rapidly dividing cells. The

most frequent side effects include gastrointestinal disturbances such as vomiting, diarrhea, and reduced appetite, as well as bone marrow suppression resulting in decreased white blood cells (neutropenia), anemia, or thrombocytopenia. Alopecia (hair loss) is generally mild except in breeds with continuously growing coats. Certain drugs may also cause specific toxicities, such as cardiotoxicity (e.g., doxorubicin) or renal toxicity (e.g., cisplatin).

Basic management strategies involve preemptive use of antiemetics to control nausea, routine monitoring of blood counts before and during therapy, and dose adjustment or treatment delay if significant myelosuppression is detected. Hydration and supportive care may be provided if gastrointestinal symptoms are severe. Owners should be informed about common warning signs, such as lethargy, persistent vomiting, fever, or unexplained bruising, and encouraged to seek prompt veterinary attention if these occur.

Chemotherapeutic intervention for different types of tumours in bovines

A study conducted between 2012 and 2014 examined 59 samples suspected of neoplasia in cattle (47 samples) and buffaloes (12 samples), confirming neoplasia in 57 of them. The study found a higher incidence of tumours in cattle (78.95%) compared to buffaloes (21.05%). The tumours with the highest incidence in bovines were papilloma (21.05% of cases). This was closely followed by squamous cell carcinoma and fibroma, both accounting for 17.54%. Lymphosarcoma was next at 14.04%, and adenoma represented 7.02% of cases. Furthermore, adenocarcinoma, melanoma, and myxosarcoma each occurred in two cases, collectively accounting for 3.51% of the total tumours.

Papilloma

Reported therapeutic approaches for bovine papillomatosis include conventional chemotherapeutic and immunomodulatory treatments. Vincristine-based therapy combined with lithium antimony thiomalate, Thuja-30, and autohaemotherapy resulted in complete regression within 30–45 days. Homeopathic Thuja-30 and anthiomaline were also reported to produce substantial clinical improvement, whereas autogenous vaccination showed no cure and untreated animals showed no recovery. Ivermectin administered subcutaneously, with a repeat dose after two weeks, resulted in progressive regression of papillomas, with lesions beginning to disappear between 15 and 45 days and complete cure reported within 30–90 days. These findings indicate that several pharmacological and immunomodulatory approaches have been explored for the management of bovine papillomatosis, with variable therapeutic responses.

Two additional chemotherapeutic modalities, aside from those previously mentioned, have been reported in the literature with ambiguous results. The first is intravenous infusions of magnesium chloride, often used when lesions are few; this treatment is frequently combined with Ivermectin (Lotfalizadeh *et al.*, 2022) [9].

The second modality is a 25% magnesium sulfate solution administered intramuscularly at 0.005–0.05 g/kg (Mates, 2019).

Study	Treatment / Intervention	Outcome / Findings
Therapeutic Management of Papillomatosis in Cattle (Kumar <i>et al.</i>, 2017)	Inj. Vincristine 0.025 mg/kg IV weekly × 2 doses Inj. Lithium Antimony Thiomalate 20 mL IM × 3 doses (48 h interval) Liq. Thuja-30 5 mL PO BD × 2 weeks + Autohemotherapy (20 mL from affected animal, 10 mL SC on each side of neck weekly × 3 doses)	Complete regression within 30–45 days
Bovine Papillomatosis and its Treatment under Farm Condition (Archana <i>et al.</i>, 2019)	Homeopathic Thuja-30 (Group I) Anthiomaline (Lithium Antimony Thiomalate) (Group II) Autogenous vaccine (Group III) No treatment (Control group)	100% cure 75% reduction 0% cure No recovery observed

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Study	Treatment / Intervention	Outcome / Findings
Regression of bovine cutaneous papillomas via ivermectin-induced immunostimulant and oxidative stress (Saied, 2021)	Ivermectin 0.2 mg/kg SC (repeat after 2 weeks)	Papillomas began to disappear from day 15 to 45 post-treatment; complete cure observed within 30–90 days

Squamous cell carcinoma

Podarala *et al.* (2020) [10] evaluated the therapeutic efficacy of intralesional Bacillus Calmette–Guérin (BCG) vaccine and surgical excision combined with topical Mitomycin C in bovine ocular squamous cell carcinoma. Animals treated with intralesional BCG vaccine administered at 0, 14, 35, and 56 days (2–4 mL depending on tumour size) showed progressive reduction in tumour size, along with drying and shrinkage, particularly evident after the fourth injection. This

treatment protocol achieved 100% efficacy with no recurrence observed during a one-year follow-up period. Similarly, animals subjected to surgical excision followed by topical application of Mitomycin C (0.04%) on alternate weeks for two months demonstrated complete recovery in all cases, also with 100% efficacy and no recurrence over one year. These findings indicate that both immunotherapeutic and combined surgical-chemotherapeutic approaches are highly effective for managing ocular squamous cell carcinoma in bovines.

Group	Treatment Protocol	Outcome / Efficacy
Group I	Intralesional BCG vaccine (0, 14, 35, 56 days; 2–4 mL depending on tumour size)	Reduction in size, drying, and shrinkage after the 4th injection. 100% efficacy with no recurrence for 1 year
Group II	Surgical excision + topical Mitomycin C (0.04%, applied on alternate weeks for 2 months)	Complete recovery in all animals. 100% efficacy with no recurrence for 1 year

The management of bovine squamous cell carcinoma (SCC) includes surgical, chemotherapeutic, immunotherapeutic and physical treatment approaches. Lakshmi *et al.* (2021) [11] compared surgical excision, intralesional Bacillus Calmette–Guérin (BCG), surgery combined with autogenous vaccination, and surgery followed by topical mitomycin C in bovine ocular SCC, emphasising that treatment selection should be based on the lesion's size, location, and extent. A multimodal approach was associated with favourable disease-free outcomes.

As a chemotherapeutic approach, topical mitomycin C (0.04%) was administered following surgical excision. In contrast, cisplatin emulsified in sesame oil was evaluated as a locally administered adjunct after surgical removal of ocular and vulvar SCC. In the latter technique, the cisplatin dose was calculated according to the volume of the surgical bed at 1 mg/cm³, and the emulsion was infiltrated in parallel rows approximately 1 cm apart to ensure uniform distribution. Postoperative abscess formation was, however, reported in the majority of animals receiving cisplatin–sesame oil emulsion.

Immunotherapeutic approaches have also been explored. Hoffmann *et al.* (1981) [12] treated bovine ocular SCC using a single intramuscular injection of phenol–saline extracts prepared from allogeneic carcinomas. Among 44 carcinomas, 33 (78%) responded, including complete regression in 15 cases, with better responses observed at doses of 200 mg or more of lyophilised extract. Halleran *et al.* (2021) [13] further investigated mycobacterial cell wall stimulants as an immunotherapeutic modality for SCC, supporting the potential role of local immunomodulation in tumour management.

Physical tumour destruction using radiofrequency hyperthermia has also been investigated. This technique involved localised heating of tumour tissue to approximately 50 °C. Treatment duration varied according to tumour size and number, and repeated application was recommended for some larger lesions. Recurrence following apparent

complete remission was mainly observed at tumour margins, highlighting the importance of adequate treatment coverage.

Overall, the reviewed studies demonstrate that bovine SCC can be managed using a range of therapeutic modalities. While surgical excision remains central to treatment, adjunctive chemotherapy, immunotherapy and localised hyperthermia may improve local tumour control and provide alternative options depending on tumour characteristics and clinical feasibility.

Oral tumours

Oral tumours have been reported in buffaloes aged 3.5–10 years, with all 11 reported cases occurring in female animals. The lesions were predominantly located in the rostral mandible ($n = 8$), followed by the right mandibular gingiva ($n = 2$) and lower lip ($n = 1$). Histopathologically, ameloblastoma was the most frequently reported tumour ($n = 4$), followed by fibroma ($n = 1$), myxoma ($n = 1$), fibromyxoma ($n = 1$), papilloma ($n = 1$), ameloblastoma with fibroma ($n = 1$), fibromyxochondroma with actinomycotic granuloma ($n = 1$), and granulation tissue with hyperplastic epithelial cells ($n = 1$). Thus, the reported cases demonstrated considerable histopathological diversity, with a marked predominance of lesions involving the mandibular region (Kumar *et al.*, 2022) [14].

The reported therapeutic approaches for oral tumours included surgical excision, vincristine, Anthiomaline®, and potassium iodide, either alone or in combination. A case of odontoma with secondary actinomycosis showed reduction in tumour size following Anthiomaline® and potassium iodide treatment without complications. In Murrah buffaloes with oral tumours, surgical excision combined with vincristine and Anthiomaline® was associated with recovery in most treated animals, although recurrence and mortality were also reported. Comparative treatment observations further indicated that vincristine was useful for smaller tumours, whereas combination therapy with Anthiomaline® was reported to provide better results; surgical debulking was suggested for larger tumours.

Study / Reference	Treatment(s) Used	Findings / Remarks
Medicinal management of odontoma with secondary actinomycosis in buffalo (Kumar <i>et al.</i> , 2021)	Inj. Anthiomaline® 20 mL IM on alternate days × 6 doses; Potassium iodide 15 g PO × 15 days	Decrease in tumour size after 15 days without complications
Diagnosis and therapeutic management of oral tumours in Murrah buffaloes (Kumar <i>et al.</i> , 2022)	Surgical excision; Inj. vincristine sulphate 0.75 mg/m ² IV weekly × 4–6 doses; Inj. Anthiomaline® 15–20 mL IM on alternate days × 6 doses	8 recovered, 2 died and 1 recurrence. Chemotherapy was reported as effective for small tumours, while surgical debulking was recommended for large tumours

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Study / Reference	Treatment(s) Used	Findings / Remarks
Update on oral tumours in bovine (Kumar <i>et al.</i> , 2019)	Vincristine alone versus vincristine + Anthiomaline	Vincristine was effective for small tumours; combination therapy gave better results than vincristine alone

Lymphosarcoma

Reported therapeutic approaches for bovine lymphosarcoma include systemic chemotherapy and intralesional immunotherapeutic treatment. Vincristine sulphate at 0.02 mg/kg IV produced a progressive reduction in lymphoid enlargement, although severe leucopenia was observed on day 7; by day 14, further reduction in enlargement and return of the prescapular lymph nodes toward normal were reported. L-asparaginase administered intravenously at 60,000 IU over four

treatments improved weakness, ataxia, lymph node enlargement and exophthalmos without reported adverse effects, although the treated animal survived for 57 days. Intralesional administration of *Nocardia rubra* cell-wall skeleton resulted in complete regression of 7 of 10 nodules, with reduced tumour-associated antigen-positive cells and prolonged suppression of these cells in one animal. Overall, these reports demonstrate variable responses to systemic chemotherapeutic and intralesional immunotherapeutic approaches in bovine lymphosarcoma.

Study / Treatment	Protocol / Dosage	Outcome / Response	Clinical Findings (Day 7)	Clinical Findings (Day 14)
Vincristine sulphate (Jhambh <i>et al.</i> , 2014)	0.02 mg/kg IV (diluted in 1 L normal saline)	—	Decrease in Size of lymphoid enlargement; severe leucopenia ($1.37 \times 10^6/\text{mm}^3$)	Further reduction of lymphoid enlargement toward normal; slightly congested conjunctival mucous membrane; prescapular lymph nodes returned to normal
L-asparaginase treatment (4-yr-old Holstein cow) (Masterson, 1988)	L-asparaginase 60,000 IU IV (total of 4 treatments)	Improved clinical signs (↓ weakness, ↓ ataxia, ↓ lymph node size, ↓ exophthalmos); no side-effects; animal survived 57 days	—	—
<i>Nocardia rubra</i> cell wall skeleton (N-CWS) (Onuma, 1989)	0.5–4 mg per nodule injected intralesionally (2–3 injections given at 2–4 week intervals)	Complete regression in 7 of 10 nodules; ↓ TAA-positive cells; in one animal, TAA remained low for ≥ 280 days	—	—

Recent advances

Recent advances in cancer therapeutics have increasingly focused on molecularly targeted approaches, including RNA interference (RNAi)-based gene knockdown therapy. Mohan *et al.* (2017) [15] proposed using small interfering RNA (siRNA) and short hairpin RNA (shRNA) to target and suppress genes involved in tumour growth and angiogenesis in veterinary neoplasia. RNAi mediates sequence-specific degradation of target messenger RNA, thereby reducing the expression of selected genes associated with tumour progression. Synthetic siRNA produces transient gene silencing, whereas shRNA-expressing vectors may provide a more sustained inhibitory effect.

The Sema4D–Plexin-B1 signalling pathway is a potential molecular target because it is involved in tumour-associated angiogenesis. The proposed strategy involves shRNA-mediated downregulation of Sema4D, which may inhibit tumour vascularisation and consequently restrict tumour growth. The authors suggested that Sema4D knockdown could complement conventional antiangiogenic therapies, particularly in tumours resistant to VEGF-targeted approaches.

However, this approach remains largely experimental and prospective in veterinary oncology. Although RNAi-based knockdown therapies have shown potential in human cancer research, their clinical application in animals has not yet been established because of challenges related to delivery systems, cost, technical expertise, infrastructure and the need for further species-specific research. Recent case reports and pilot studies in companion animals have begun to explore safe delivery mechanisms and efficacy of RNAi therapeutics in selected tumour types, such as canine melanoma and feline fibrosarcoma, but large-scale clinical trials remain limited. Some ongoing veterinary clinical trials are investigating nanoparticle-mediated delivery of siRNA to target tumour angiogenesis and growth in dogs, although published results are still pending. Thus, targeted gene silencing represents a

promising future direction for developing more precise and personalised therapeutic strategies for animal neoplasia, including potentially SCC.

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