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Canine Transitional Cell Carcinoma: What's New?

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KEY POINTS

- A molecular approach is available to non-invasively aid in detecting patients suspected of having TCC/UC and breeds predisposed to TCC/UC, allowing the approach to management to be determined earlier.
- Dog breed and environmental elements are predisposing factors for TCC/UC.
- Biological phytochemical compounds that may support approaches to traditional multimodal management have been identified.
- A bioavailable sulforaphane production supplement (Avmaquin™) has been shown to increase sulforaphane in the bloodstream of dogs.

Detection: Commercially Available Molecular Test

The most common cancer of the canine urinary tract is transitional cell carcinoma (TCC), also known as urothelial carcinoma (UC).[1,2] It is estimated to represent 1% to 2% of all canine cancers,[3] with increasing prevalence seen at university teaching hospitals.[1] Risk factors for TCC/UC include obesity, female sex, and exposure to specific environmental agents such as herbicide-treated lawns.[1,4,5] An elevated incidence has been observed in a number of dog breeds, including Scottish terriers, Shetland sheepdogs, West Highland white terriers, wire fox terriers, and beagles.[1,3,6,7]

TCC/UC is often identified following observation of lower urinary tract signs (eg, stranguria, pollakiuria, hematuria). These signs may also result from other more common bladder health issues such as UTI, polyps, prostatitis, and bladder stones.

Because bladder infections are a common reason for dogs to be presented with lower urinary tract signs, first-line management often involves antibiotic and/or anti-inflammatory medications, with recurrence of signs eventually creating concern for TCC/UC.[1,3,6,8,9]

Histopathology is the gold standard for detection of TCC/UC, but this approach requires invasive and costly procedures. The use of traditional, noninvasive options relies on cytologic identification of abnormal epithelial cells in urine specimens, which may be misleading and contribute to delayed detection.[5,10,11] Once TCC/UC is diagnosed, management options vary and can include cyclooxygenase inhibitors, cytotoxic chemotherapy, radiation therapy, and surgery.[5] Prognosis is generally guarded.[2,12]

Molecular studies of canine TCC/UC have identified the presence of a single base mutation in the canine *BRAF* gene, which has been detected in ≈85% of cases studied.[13,14] The remarkably high prevalence of this mutation in patients with TCC/UC as compared with patients with other cancers[15] has facilitated development of a commercially available molecular test with high sensitivity and specificity using a noninvasive (free-catch) urine sample.[13] Further, using a technical approach that is not impacted by the presence of blood, protein, and bacteria in the urine enhances the utility of this approach to aid detection of TCC/UC for dogs with overt clinical signs.[13,16] Earlier detection may increase the time for appropriate intervention, thus enhancing opportunities to potentially improve outcomes. Moreover, detection of low-level mutation, associated with preclinical cases of TCC/UC, provides opportunities for veterinarians to consider the most appropriate management, which could improve quality and duration of life of these patients.

In addition to earlier detection, it is critical to focus on measures that optimize canine urinary tract health, such as avoiding environmental risk factors, maintaining a healthy weight, and ensuring a healthy diet, including cruciferous vegetable supplementation.[4,7,17] Studies of dietary supplements aimed at supporting management of human cancers, bladder included, suggest that sulforaphane, found in raw cruciferous vegetables, may provide added benefits to humans, with potential translation to canine patients.[18-24]

What Is Sulforaphane?

Cruciferous vegetables, most notably broccoli, contain crucial isothiocyanates, which produce a key compound: sulforaphane (SFN).[25] It releases into the body upon breaking down from its precursor, the phytonutrient glucoraphanin. Although glucoraphanin occurs in all parts of the broccoli plant, it is concentrated in the seeds and sprouts.[26] The introduction of the plant enzyme, myrosinase, from intracellular vesicles catalyzes the hydrolysis of glucoraphanin to SFN.[26] This breakdown process initiates through damage to the plant (eg, chewing, chopping, cutting).

Mechanisms of Action

The primary mechanism through which SFN supports cellular health is by direct antioxidant effects or by indirectly inducing phase 2 detoxifying enzymes by upregulating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, thereby reducing oxidative stress.[18,27] Nrf2 has been shown to support cells and tissue from various insults by increasing the expression of a number of these phase 2 enzyme genes.[28] Phase 2 detoxification enzymes (eg, NQO1, glutathione reductase, glutathione-S-transferases) play an important role in detoxifying potential mutagenic toxicants. Under physiologic conditions, Nrf2 is primarily localized in a complex with Kelch-like ECH-associated protein 1 (Keap1). Keap1 is inactivated upon exposure to oxidative stress, which dislodges Nrf2 and allows Nrf2 to transfer into the nucleus to activate phase 2 enzyme genes.[28] SFN is one of the most potent phytochemicals that can activate the Nrf2 pathway.[26]

Sulforaphane Research

SFN has been the subject of extensive research identifying major supportive pathways of cellular activity, leading to the initiation of numerous studies indicating its role in aiding cellular health in humans.[23,29,30] SFN research in veterinary medicine is emerging, with further research warranted to identify clinical applications. When administered to healthy dogs in a study, a broccoli sprout supplement containing glucoraphanin and active myrosinase (the precursors to SFN) showed absorption in plasma and urine that remained detectable at 24 and 48 hours, respectively, postconsumption.[31] Researchers also noted a decrease in activity of histone deacetylase, a chromatin-modifying enzyme that has been shown to have increased activity with certain mutagenic cells in the body, at 24 hours postadministration.[31] A study of SFN supplementation in dogs with compromised lymphatic health was associated with significant changes in lymph node proteome.[32] The proteins impacted by SFN involved immune health and oxidative stress responses. A study using canine cell lines demonstrated diminished cell invasion in the cells treated with SFN.[18]

Studies of the pharmacodynamic and pharmacokinetic properties of an oral glucoraphanin and myrosinase supplement supporting sulforaphane production were performed in beagle dogs.[33] Blood samples of 4 dogs administered a tablet containing a proprietary blend of glucoraphanin and active myrosinase (Avmaquin™) orally once a day for a 3-day period revealed induced phase 2 enzyme gene expression at all time points after administration and increases in plasma SFN levels.[33] Furthermore, administration of glucoraphanin in a fasted state has been shown to significantly increase SFN plasma levels as compared with administration with food.[34] Results from this study showed higher total peak plasma SFN than a recently published study.[31]

Supplemental Options

Consumption of specific levels of SFN from routinely harvested broccoli or sprouts alone can be difficult to achieve due to variations in environment, plant genotype, and harvesting methods. In addition, because heat can damage SFN hydrolysis, variation in cooking methods can lead to inconsistencies in amounts.[26,35] Sprouts can contain ≥100 times more phytonutrients than mature plants,[26,36] but broccoli is particularly sensitive to metals in contaminated soil, which can affect plant development.[37]

Glucoraphanin, the precursor of SFN, is a comparatively stable molecule that can be converted to SFN by exposure to myrosinase, making it a good candidate for dietary supplementation. Although glucoraphanin occurs in all parts of broccoli plants, it is most abundant in the sprouts and seeds.[26] Seed extraction of glucoraphanin and myrosinase ensure a stabilized, consistent source of SFN as compared with cruciferous vegetable supplementation.

Future Directions

With a commercially available detection method for dogs with TCC/UC issues, veterinarians may be able to intervene more appropriately and target management of patients. SFN has been extensively studied for its mechanisms of action and shown to be of benefit in various human studies. As SFN research continues to emerge in veterinary medicine, additional studies are warranted to assess potential benefits of SFN for clinical applications.

For references, please visit **cliniciansbrief.com/article/clinical-notes-canine-transitional-cell-carcinoma-whats-new**

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