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Preliminary results of intraoperative photodynamic therapy with 5-aminolevulinic acid in dogs with prostate carcinoma

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Abstract

Six client-owned dogs with prostate carcinoma were treated with a combination of (1) partial subcapsular prostatectomy using an Nd:YAG laser, (2) intraoperative photodynamic therapy using a halogen broad band lamp after local administration of a photosensitiser, and (3) systemic treatment with meloxicam. Median survival time was 41 days (range 10–68 days), which compared negatively with previous reports of subtotal laser prostatectomy combined with topical interleukin-2 administration, and photodynamic therapy alone. Despite treatment, the disease progressed locally, causing signs of stranguria to recur, and in the form of distant metastases. The recurrence of clinical signs due to the primary tumour despite photodynamic therapy is probably largely explained by insufficient penetration of light into the tissue. Better results may be obtained using other light sources (e.g. laser) and alternative techniques of light delivery, such as fibres or catheters allowing interstitial diffusion of light.

Keywords: Prostate carcinoma; Photodynamic therapy; Dog; Intraoperative; ALA

Introduction

Photodynamic therapy (PDT) involves the topical or systemic administration of a photosensitiser followed by the delivery of light to the target area. The interaction of light with the intracellular photosensitiser causes the release of oxygen radicals leading to cell death (Moore et al., 1997). The relative selectivity of the technique lies in the topical administration to or the selective uptake by neoplastic tissue, as well as in the localised delivery of light (Moore et al., 1997).

One of the best studied photosensitisers is 5-aminolevulinic acid (ALA). ALA has been used successfully for both photodiagnosis (Baumgartner et al., 1996) and photodynamic treatment (Kennedy et al., 1990, 1996) of neoplastic lesions. ALA itself is not a photosensitiser but it induces the formation of protoporphyrin IX and other photoactive porphyrins (PAP) (Peng et al., 1997). Ester derivatives of ALA have the advantage of being more lipophilic than ALA allowing them to penetrate better through lipid membranes and into tissues (Casas and Batlle, 2002; Marti et al., 1999). ALA esters do not increase the level of PAP formed in the tissue compared to ALA, but increase the confinement of PAP to the location of the administration making them best adapted to topical rather than systemic administration (Perotti et al., 2002, 2003).

The first experiences with the use of PDT as a treatment modality for neoplasia in companion animals were reported in the 1980s (Cheli et al., 1984, 1987). These initially promising results led to growing interest in the technique which has subsequently been used to treat many different types of canine and feline tumours, including skin tumours such as intraoral and cutaneous squamous cell

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carcinoma (SCC) (Frimberger et al., 1998; Roberts et al., 1991), mast cell tumours, mixed mammary gland tumours (Roberts et al., 1991), and haemangiopericytomas (McCaw et al., 2001). Other reports have presented cases of oesophageal SCC (Jacobs and Rosen, 2000) and prostate carcinoma (Lucroy et al., 2003) treated with PDT.

Canine prostate carcinoma (PCA) is a rare but consistently aggressive tumour that frequently metastasises (Cooley and Waters, 2001). In humans, PCA is mostly treated by androgen ablation or radical prostatectomy (Damber, 2005; Damber and Khatami, 2005), but PCA in dogs requires other forms of treatment. Canine PCA does not respond to androgen ablation. In fact, PCA occurs more commonly in castrated males (Teske et al., 2002). In addition, radical prostatectomy is complicated by a high prevalence of incontinence (Goldsmid and Bellenger, 1991).

Subtotal intracapsular prostatectomy can relieve clinical signs without causing incontinence (L'Eplattenier et al., 2006), however since tumour removal is incomplete with this technique, local control of the neoplastic tissue remaining around the urethra and in the dorsal portion of the prostate is critical to prevent recurrence of clinical signs and to increase survival times. Recently, partial prostatectomy using Nd:YAG laser dissection was combined with local injections of interleukin (IL)-2 and postoperative systemic treatment with the cyclo-oxygenase (COX)-2 inhibitor meloxicam to manage PCA in eight dogs (L'Eplattenier et al., 2006). The dogs survived up to 8 months postoperatively (median 103 days, range 5–239 days) and most were eventually euthanased because of recurring clinical signs attributed to the primary tumour (most often stranguria). In another report, a dog with PCA was successfully treated with PDT alone, and survived for 9 months after treatment (Lucroy et al., 2003), suggesting PDT may be an effective way of locally controlling PCA cell growth and may be a useful adjunct to surgical debulking of the tumour.

This present study reports the results of intraoperative PDT using topically administered hexyl aminolevulinate, following partial subcapsular prostatectomy in six dogs. We hypothesised that PDT would be at least as effective as local administration of IL-2 in controlling PCA locally and preventing recurrence of clinical signs after subtotal prostatectomy.

Materials and methods

Animals and preoperative assessment

Six client-owned dogs were included in the study. Inclusion criteria were echographic signs of prostatomegaly, including abnormal structure and shape of the prostate, with or without enlargement of the sublumbar lymph nodes, cytologically-confirmed diagnosis of prostate carcinoma, and the owner's informed consent. Regional lymph nodes were not assessed cytologically before surgery. Patients were excluded from the study if radiographic and/or computed tomography (CT) evaluation of the lungs and caudal axial skeleton (lumbar spine, sacrum and pelvis) revealed changes consistent with the presence of metastases.

Anaesthesia and pain management

All dogs were premedicated using medetomidine (Domitor, Pfizer, 20 μg/kg IV, redosed at half the dose every hour), then anaesthesia was induced using propofol (PropoVet, Abbott, 1–2 mg/kg IV, to effect). The dogs were intubated and anaesthesia was maintained with isoflurane (IsoFlo, Abbott, <1% end-tidal concentration in 50% air and 50% O_2). The dogs were given an infusion of Ringer's lactate (Braun Melsungen AG, 5 mL/kg per hour). Postoperative analgesia was provided by a combination of buprenorphine (Temgesic, Schering-Plough, 20 μg/kg SC four times daily until the animals were released from the clinic) and the non-steroidal anti-inflammatory drug (NSAID) meloxicam (Metacam, Boehringer Ingelheim, 0.2 mg/kg PO once on the day of surgery, then 0.1 mg/kg PO once daily for the rest of the dog's life).

Surgical technique

All animals underwent a surgical procedure as described previously (L'Eplattenier et al., 2006). The technique involved a subcapsular partial prostatectomy, sparing the urethra and the dorsal aspect of the prostate capsule including the neurovascular structures essential to the normal function of the urethral sphincter. Preoperatively, a urethral catheter was placed to allow localisation of the urethra during the procedure. Antibiotic prophylaxis was provided by administering 20 mg/kg amoxicillin and clavulinic acid IV at induction of anaesthesia.

The prostate was approached via a caudal midline coeliotomy. The bladder was retracted cranially and periprostatic fat was dissected from the prostate to allow visualisation of the ventral portion of the prostate capsule. Using a continuous wave Nd:YAG laser (Medilas 40 N, MBB-Medizintechnik) with a 600 μm optical fibre (Ultraline, Heraeus LaserSonics) the ventral part of the prostatic capsule was incised along the midline. Prostate tissue was bluntly separated from the capsule then segments of parenchyma were removed using laser dissection to control haemorrhage. Samples of prostate tissue were submitted for histopathological exam to confirm the preoperative cytological diagnosis of PCA. The urethra was left intact and prostate tissue was removed on each side of the urethra as far dorsally as possible.

Photodynamic therapy

The photosensitiser hexyl aminolevulinate hydrochloride and the halogen PDT lamp (CureLight BroadBand) were supplied by PhotoCure ASA. After the subtotal prostatectomy, 10 mL of the reconstituted photosensitiser (8 mM) were administered to the prostate by injection into the remaining periurethral and subcapsular prostate tissue. The photosensitiser was left for 1 h before light delivery in order to allow for uptake and metabolism by the PCA cells. After 1 h, the PDT lamp was calibrated following the instructions of the manufacturer and red light (570–670 nm) was delivered to the prostate at a dose of 75 J/cm^2 (light intensity 200 mW/cm^2, as described in the User Manual). During light delivery, the prostate capsule was maintained open with a small Weitlaner retractor in order to facilitate optimal penetration of light into the remaining tissue around and dorsal to the urethra. After completion of light treatment, the edges of the capsule were trimmed and the capsule was sutured ventrally over the urethra without leaving any dead-space, using a continuous pattern of synthetic monofilament absorbable material (polyglecaprone 25, size 3–0, Monocryl, Johnson & Johnson). The abdomen was closed in a routine manner.

Postoperative management and follow-up

All patients were treated postoperatively with a systematic administration of meloxicam (Metacam, Boehringer Ingelheim, 0.2 mg/kg on the day of surgery, then 0.1 mg/kg PO once daily for life). They were examined 1 month postoperatively, then every other month. On each follow-up visit, chest radiographs were taken and an ultrasound examination of the abdomen was performed.