Photodynamic therapy and diagnosis: Principles and comparative aspects

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Abstract

Photodynamic therapy (PDT) is an evolving method of treating superficial tumours that is non-invasive and carries minimal risk of toxicity. PDT combines tumour-selective photosensitiser dyes, tissue oxygen and targeted illumination to generate cytotoxic reactive oxygen species (ROS) within the tumour. In addition to directly acting on tumour cells, PDT damages and restricts tumour microvasculature, and causes a local inflammatory response that stimulates an immune response against the tumour. Unlike surgery or radiotherapy the surrounding extracellular matrix is unaffected by PDT, thus tissue healing is excellent and PDT seldom scars. This, combined with the ease of light application, has made PDT a popular treatment for cancers and pre-cancers in humans. Moreover, because photosensitiser dyes are fluorescent and selectively accumulate in tumour tissues, they can additionally be used to visualise and discriminate tumour from normal tissues, thereby improving the accuracy of tumour surgery.

In veterinary practice, PDT has been used successfully for treatment of superficial squamous cell carcinoma of the feline nasal planum; urinary tract, bladder and prostate neoplasia in dogs; and for equine sarcoids. The purpose of this article is to make a comparative review of the current literature on PDT in human and veterinary medicine, to provide a basis for future development of PDT in veterinary medicine.

Key words

Photodynamic therapy; cancer.

Introduction

Photodynamic therapy (PDT) involves administration of a photosensitiser drug, or a pro-drug, which selectively accumulates in target cells, followed by local illumination of the lesion with visible light (Luksiene, 2003; Wachowska et al., 2011). It is a minimally invasive therapeutic technique used in the management of various cancerous and pre-malignant diseases. The photosensitiser can also be visualised in tumour cells using an appropriate set of imaging filters to provide a means of tumour detection (Hefti et al., 2010, Mowatt et al., 2011, , Nguyen and Tsien 2013, Allison 2016).

In addition to cancer treatment, PDT has been used for the treatment of microbial infections (Kharkwal et al., 2011, Sharma et al., 2012, Wardlaw et al., 2012), including veterinary applications in dogs (Fabris et al., 2014) and sheep (Sellera et al., 2016). PDT has also been used for light-triggered uptake of pharmaceuticals that would otherwise become entrapped and destroyed within cellular endosomes (photochemical internalisation, PCI; reviewed by Selbo et al., 2015 and Madsen 2016). However, the focus of this review will be on the uses of PDT in cancer treatment and diagnosis.

The origins of PDT can be traced back to ancient Egypt, where photosensitizing plant pigment extracts were applied to the skin and exposed to sunlight, as a treatment for psoriasis (Daniell and Hill 1991). The use of PDT for treatment of various human skin cancers was first investigated in the 1970's by Dougherty et al (1978). Dougherty's use of a haematoporphyrin derivative was based on pioneering work of Policard et al., (1924) who demonstrated that porphyrins were preferentially distributed into malignant rather than normal tissues. The technique was slow to gain acceptance because the 'first generation' photodynamic agents were slow to clear from normal cells with the result that treated human patients had to remain out of bright light (e.g.sunlight) for several weeks to avoid severe skin reactions. However, the potential for the technique in treating locally advanced carcinomas of the head and neck (Wile et al., 1984), bladder (Misaki et al., 1983), oesophagus and bronchus (Cortese and Kinsey 1984) outweighed this caveat and stimulated further research.

The availability of haematoporphyrin derivatives with faster tissue clearance times stimulated more interest in PDT and numerous human clinical trials have now been published showing encouraging results with photosensitizing dyes administered topically or systemically (orally or intravenously) or instilled into hollow organs (e.g. bladder). A limited number of veterinary studies have been published, also showing promise. A previous review of PDT in veterinary medicine was published in 2013 (Buchholz and Walt, 2013), since then further advances have been made. The purpose of this review is to describe the basic principles of PDT and discuss the clinical application of PDT in humans and animals.

Fundamentals and mechanisms

There are three basic requirements for PDT; (1) a compound with photosensitising properties (photosensitiser, PS), (2) a source of visible light and (3) oxygen. The photosensitizer is a chemical / dye that selectively accumulates in malignant tissues and can be activated by visible light. Energy from the light-excited PS is transferred to oxygen molecules (O_2) to give reactive oxygen species (ROS), notably singlet oxygen ($^1O_2$) and superoxides, that damage biological molecules, initiating a cascade of biochemical events culminating in damage and death of neoplastic cells (Fig. 1) (Dougerthy et al., 1998, Juzeniene et al., 2007). Increasing tissue oxygenation can lead to increased ROS formation during PDT and improved outcomes (Maier et al., 2000).

The mechanisms by which different photosensitisers localise selectively in malignant tissues are complex and not fully understood. Physical factors, such as increased vascular permeability and poor lymphatic drainage in tumours, coupled with an affinity for proliferating endothelium likely contribute to their accumulation in tumours (Dougherty et al., 1998).

Three main processes by which ROS contribute to the destruction of tumours by PDT are direct cellular damage, indirect vascular shutdown and activation of immune response against tumour cells (Dougherty et al., 1998, Dolmans et al., 2003, Solban et al.,2006). Direct damage to tumour cells can result in cell death by both programmed (apoptotic) pathways and non-programmed (necrotic) pathways (Oleinick et al., 2002; Igney and Krammer 2002, Allison and Moghissi 2013a). Generally, when the light intensity is low, apoptotic death may be initiated (Agarwal et al., 1991, Allison and Moghissi 2013b). At higher light intensities, tumour cells are rapidly ablated by necrosis due to destruction of cellular and subcellular membranes. This also leads to release of cytokines and lysosomal enzymes (Henderson and Fingar 1987) causing damage to cells nearby, the bystander effect (Dahle et al., 1997, Allison and Moghissi, 2013a). Release of inflammatory mediators from the treated region stimulates activation of leucocytes including neutrophils and macrophages and significant tumour cell death occurs through these activated immune cells (Coutier et al., 1999; Gollnick et al., 2003, Castano et al., 2006). This observation has led to the development of combination therapies of PDT with immunotherapy, by including immunoadjuvants against tumour-specific epitopes (Qiang et al., 2008, Kleinovink et al., 2015).

PDT also mediates a vascular effect within tumours (McMahon et al., 1994, Abels, 2004). Neovascular tumour endothelial cells may accumulate higher levels of PS than normal endothelium (Debefve et al., 2011) and following PDT, microvascular collapse can be observed and can lead to severe and persistent post-PDT tumour hypoxia (Star et al., 1986, Henderson et al., 1987, Chen et al., 2003). PDT may also lead to vessel constriction via inhibition of the production or release of nitric oxide by the endothelium (Gilissen et al., 1993).

An important clinical consideration is effective analgesia. In humans PDT produces a sensation of stinging or burning during illumination, especially in sensitive areas such the face, and scalp (Halldin et al., 2011, Chaves et al., 2012). Treatment of large skin areas generally produces more pain than smaller areas (Grapenglesser et al., 2002, Hallidin et al., 2011, Chaves et al., 2012).

Photosensitizers for PDT

Photosensitising (PS) agents are natural or synthetic chemicals that transfer light energy to neighbouring molecules, importantly to dissolved oxygen (Allison et al., 2004). Most of the photosensitizers used in cancer therapy are based on a tetrapyrrole structure, similar to that of the protoporphyrin contained in haemoglobin. In clinical practice, a successful PS agent is: nontoxic until light activated, hydrophilic for easy systemic application, activated by a clinically useful light wavelength, and reliably generates a photodynamic reaction (PDR). It also concentrates in tumours, clears normal tissue quickly, and is eliminated from the patient relatively rapidly (Allison and Moghissi 2013a).

The first-generation photosensitizer, haematoporphyrin derivative (HPD) was a mixture of various monomers, dimers, and polymers of haematoporphyrin (Allison and Moghissi 2013a). The commercially available product, porfimer sodium, marketed under the tradename Photofrin was experimentally used in healthy dogs (Tochner et al., 1991; Panjehpour et al., 1993) and a canine glioma model (Whelan et al., 1993). It was approved for treatment of early stage of human lung cancer in 1998 and for Barrett's esophagus in 2003. The clinical application of Photofrin has been limited by two factors: its absorption peak occurs at 630 nm, too short a wavelength to allow deep penetration of light in tissue. Secondly, Photofrin results in cutaneous photosensitivity lasting up to 6 weeks (Zhu and Finlay, 2008).

These limitations stimulated the development of a second generation of photosensitizers with improved efficiency of ROS generation, more rapid clearance, fewer side effects, and absorption peaks at longer wavelengths (>630 nm red light) where the tissue penetration of light is deeper. One such second-generation photosensitiser is 5-aminolevulinic acid (ALA), a naturally occurring pro-photosensitiser and precursor for the biosynthesis of heme. For therapeutic purposes, ALA is administered topically (Morton et al., 2008, 2013), orally (Muller and Wilson, 2006), or intralesionally (Hage et al., 2007; Kim et al., 2012) and enters into all cells; although uptake is potentiated by transporters of beta-amino acids and GABA (Rud et al., 2000), highly expressed on some cancer cells and neurons (Zhang et al., 2013). ALA is then metabolised to the red-fluorescent photosensitiser protoporphyrin IX (PpIX, absorption 635 nm) and finally to non-fluorescent heme (Ajioka et al., 2006, Allison and Moghissi 2013a). This final step relies on ferrochelatase to add Fe^{2+} to PpIX and this rate-limiting enzyme is often deficient in cancer cells (Kemmner et al., 2008). Thus, in the presence of excess ALA, cancer cells that combine high ALA uptake with low PpIX destruction will accumulate PpIX photosensitiser (Collaud et al., 2004). Clinical advantages of ALA treatment include rapid clearance of PpIX from the tissue within 12 hours, resulting in short-lived cutaneous photosensitivity. In human patients ALA has been used for the treatment of T cell lymphoma (Coors et al., 2004), basal cell carcinoma (Kim et al., 2012) squamous cell carcinoma (SCC) and other head and neck cancers (Grant, et al., 1993, Morton et al., 1996). In veterinary medicine, ALA has been used to treat SCC in a cow (Hage et al., 2007) and in cats (Bexfield et al., 2008), sarcoids in horses (Gustafson et al., 2004, Golding et al., 2017) and transitional cell carcinoma in dogs (Lucroy et al., 2003a,b). See Tables 1 and 2.

The hydrophilic nature of ALA limits its ability to deeply penetrate intact skin and thereby restricts the use of topically applied ALA-PDT to the treatment of superficial diseases, where the tissue structure is disorganised. To overcome this limitation, ALA esters that are less hydrophilic than the parental compound have been developed. The methyl ester of ALA, methyl-aminolevulinate (MAL, Metvix, or Metvixia), was approved by the US Food and Drug Administration for PDT treatment of actinic keratosis in 2004 and has shown good results in treatment of equine sarcoids (Kemp-Symonds 2012, Golding et al., 2017). Hexaminolevulinate, the n-hexyl ester of ALA, (HAL, Hexvix, Cysview) which is converted to PpIX 50–100 times more efficiently than ALA, was licensed in US in 2010 for the detection of human bladder cancer (Furre et al., 2005). Hexaminolevulinate has also been used intra-operatively in a PDT model in dogs with prostate carcinoma (L'Eplattenier et al., 2008).

Several other second-generation photosensitisers have been, or are in the process of being developed, each with slightly different origins and characteristics. These include m-tetrahydroxophenyl chlorine (m-THPC, Foscan); 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a (HPPH, Photochlor); palladium bacteriopheophorbide (Padoporfin, TOOKAD) and its more water-soluble monolysotaurine derivative (Padeliporfin, TOOKAD-Soluble); motexafin lutetium (Lu-Tex, Lutrin); and Verteporfin (Visudyne). The advantages and indications for these newer agents are summarised in Table 1.

Photosensitisers for diagnosis

Photodynamic diagnosis (PDD) uses the fluorescence of photosensitisers to identify tumour tissue in situ. PDD fits within the broader category of Fluorescence Guided Surgery (Allison 2016). The distinction being that, by increasing the illumination intensity or duration, PDD can become PDT. However, whilst the generation of singlet oxygen by photosensitisers is essential for PDT, these same reactive species can damage the photosensitiser and render it non-fluorescent.

ALA has been trialled for PDD in eleven different human tumour types (Nokes, 2013), and is licensed in humans for intraoperative margin assessment in glioma (Hefti et al., 2010, Stummer et al., 2006) and the n-hexyl derivative for bladder cancer (Kausch et al., 2010, Mowatt et al., 2011). Each of the major surgical microscopy and endoscopy manufacturers (Leica, Olympus, Storz, and Zeiss) have specialized imaging equipment for intraoperative PDD for human surgery. Research versions are available for animal models (e.g. Solaris system, Perkin Elmer). However, relatively little work has been done on translating human PDD to veterinary surgery. Veterinary examples include intraoperative cancer imaging and staging in dogs (Knapp et al., 2007, Cabon et al., 2016, Osaki 2016), and image-giuded surgery in cats (Wenk et al., 2013). The next generation of agents for photodiagnosis are generally based on near infra-red dyes, which allow deeper views into tissues, sometimes complexed with tumour-targeting peptides or antibodies (Luo et al., 2011, Wenk et al., 2013).

Light sources and delivery systems

The primary requirement when treating lesions with PDT is to ensure that sufficient, homogenous light is delivered to the target tissue. Each PS has an optimal wavelength and intensity (fluence) of light for activation (Sibata et al., 2001). Choice of light source should therefore be based on PS absorption (fluorescence excitation and action spectra), location, size and accessibility of lesions, and tissue characteristics. The clinical efficacy of PDT is dependent on complex dosimetry: total light dose, light exposure time, and light delivery mode (single vs. fractionated or even metronomic). The fluence rate also affects PDT response (Henderson et al., 2006) and as demonstrated in tumour bearing cats by Hahn et al. (1998).

The wavelength of light used for PDT is typically in the range between 600–800 nm, the ‘therapeutic window’ (Wilson and Patterson, 1990). In this wavelength range, the energy of each photon is sufficient (1.5 eV) to excite the photosensitizer and yet is low enough to allow the light to penetrate up to 2 cm into the tissue (Zhu and Finlay, 2008).

The development of light sources and delivery devices with the appropriate dosimetric parameters are key components for the clinical application of PDT. Accurate delivery of the light to the tumour tissue can be accomplished by a variety of light sources and fibre optic delivery devices. Lasers have been one of the main light sources used in PDT. Modern diode lasers are portable and do not require specialized electrical supply or water cooling, providing excellent stability of output power over long periods of time (Mang, 2004). Diode lasers have been approved for use with Photofrin in oesophageal and lung malignancies at 630 nm and at 652 nm for Foscan (Yoon et al., 2013).

Alternatives to laser technology are non-coherent light sources (Reeds et al., 2004) and light emitting diodes (LEDs), the latter where light is produced by a solid-state process called electroluminescence. LEDs are compact, lightweight and require significantly less energy than lasers. LED systems are capable of output powers up to 150 mW/cm^2 over a 3 cm x 3 cm area. LEDs have been manufactured with various light output wavelengths, such as 630, 670, and 690 nm, which can be used in PDT procedures for flat surface illumination (Mang, 2004 and 2009). Light delivery for treatment of large surface areas, such as treatment of skin diseases, may also be effectively accomplished using broad-spectrum fluorescent lamps (Marcus and McIntyre, 2002). However, LEDs have been shown to be more effective than fluorescent lamps for PDT treatment of squamous cell carcinoma (Novak et al., 2016). One obvious source of light for PDT is the sun, and several recent studies have demonstrated the effectiveness of daylight PDT (reviewed by See et al., 2016). Daylight PDT has obvious potential for veterinary skin cancers, provided the tumour is located where it will be in constant daylight.

In addition to the light source, delivery devices may be required to provide penetration of light into the target tissue (Star et al., 1992). Fibre-optic devices have been developed for PDT light delivery and dosimetry (Sterenborg et al., 2014). The most widely used fibre-optic device in PDT is a cylindrical diffusing fibre tip available in lengths of 1 - 9 cm depending on the specific application. Two light delivery methods have been developed: intraluminal irradiation using light diffusers for the lung and oesophagus, and interstitial illumination methods to deliver adequate light doses to the target tumour volume in head and neck cancers (Yoon et al., , 2013). Fibre optic delivery of PDT has been used in dogs to treat intramedullary bone tumours (Burch et al., 2009).

Photodynamic therapy and diagnosis: clinical uses in humans and animals

In contrast, to its increasing use in human medicine, the use of PDT in veterinary medicine has been relatively limited, and although results from small veterinary clinical studies have been published and despite the fact that the dog and cat have been used as a preclinical model in several studies (Lucroy et al., 1999, 2003b, Griffin et al., 2001, Panjehpour et al., 2002, Tanabe et al., 2004), PDT is not well established as a treatment option for tumour bearing animals to date. The main indication currently is in treatment of in situ carcinoma/SCC in cats. Other possible indications are urinary tract neoplasia and glioma in dogs and SCC and sarcoids in horses (Buchholz and Walt, 2013). The following is a comparative review of the clinical experience of application of PDT in human and veterinary medicine to provide a basis for future development and application of the technique in veterinary medicine.

Cutaneous tumours

Carcinoma in situ / Squamous cell carcinoma (SCC)

ALA-PDT is mainly used to treat dermatological cancers in humans and several reviews of current guidelines have been published (Morton et al., 2008, 2013; Wan and Lin, 2014). The results of ALA-PDT in the treatment of human Bowen's disease (squamous cell carcinoma *in situ*) have been promising; randomized, controlled trials comparing ALA-PDT or MAL-PDT to cryotherapy (Morton et al., 1996) or 5-fluorouracil (5-FU) cream (Salim et al., 2003) reveal complete response rates of 82-100% for PDT vs 67-100% for cryotherapy or 79-94% for 5-FU at 12-24 months. The efficacy of topical ALA-PDT in the management of primary cutaneous invasive SCC is variable, with response rates of 54 – 100% reported for superficial lesions and recurrence rates ranging from 0 – 69%, but with reduced efficacy in more nodular lesions (Wolf et al., 1993; Morton et al 2002). Current evidence supports the potential of topical ALA-PDT for superficial, micro-invasive SCC but in view of its metastatic potential topical PDT cannot be recommended for invasive SCC (Morton et al., 2008, 2013).

Cutaneous in situ-carcinoma/SCC in the cat represents the main application for PDT in veterinary medicine to date (Fig. 2). A number of studies have reported response rates from 60 – 80+% and disease-free intervals of over 68 weeks, for topical and systemic PDT in cats using a variety of photosensitisers (as detailed in Table 2). As is the case in human patients, the smaller and less invasive tumours respond best to PDT (Magne et al., 1997). PDT has also been used to treat SCC in dogs (McCaw et al., 2000), horses (Giuliano 2008), a cow (Hage et al., 2007), snakes (Roberts WG et al.,1991) and a Great Hornbill (Suedmeyer et al., 2001).

Basal cell Carcinoma

PDT has been successfully employed for treatment of basal cell carcinoma (BCC) in human patients as a sole agent or in neoadjuvant setting (Berroeta et al., 2007, Rhodes et al., 2007). A 92% complete response rate was reported with topical ALA-PDT in 330 patients with superficial BCC, but the response rate dropped to 71% in patients with nodular BCC (Zeitouni et al., 2001) , and when topical PDT (with ALA or MAL) is compared to surgery for BCC, PDT consistently shows an increased recurrence rate for both superficial and nodular BCC (Basset-Seguin et al., 2008). This may be due to insufficient penetration of the photosensitizer to deeply located tumour cells when the PS is applied topically. To overcome this problem, the PS may be injected intralesionally. Twenty patients with nodular BCC were treated with ALA in 1% saline solution at estimated dose of 1 mL/cm^2 injected into the base of tumour. PDT resulted in tumour necrosis, followed by complete re-epithelization after 4-6 weeks with good cosmetic results, no histological evidence of BCC after 3 months and no recurrence during follow-up of 19.5 months (Rodríguez-Prieto et al., 2012).

Experience of intralesional injection of PS is very limited in animals. One study reported PDT in a cow with ocular SCC using intratumoural injection of ALA. A complete response was observed after 3 months and no relapse 12 months after the treatment (Hage et al., 2007). PDT has also been used for treatment of periocular SCC in horses. A pilot study was conducted using surgical resection plus PDT for periocular SCC in horses by infiltrating wound beds with HPPH prior to illumination. This combination yielded disease-free intervals of 25–68 months. The overall recurrence rate was 22% (2 of 9 horses) and for those horses where local PDT was the first and only treatment modality used, the recurrence rate was 0% (Giuliano et al., 2008).

Equine sarcoids

Although of fibroblastic rather than of basal cell origin, equine occult and nodular sarcoids form dermal nodules or plaques and as such bear some physical resemblance to the human nodular BCC. Currently there is no ‘gold standard’ treatment for equine sarcoids, however, PDT has shown promise in the treatment of these common and frustrating lesions. Several small studies have reported encouraging response rates using topical or locally injected ALA or MAL in equine occult and nodular sarcoids. For instance, Gustafson et al., (2004) found a 72% treatment response using ALA-PDT, with recurrence in 39% of lesions after 2 years (n=18). Due to their fibroblastic and bulky nature, cytoreductive surgery may significantly improve response for larger lesions. In one study, CO_2 laser excision with adjunctive MAL-PDT was reported to achieve a 93% one-year disease-free rate (Kemp-Symonds 2012). Most recently, a single application of topical ALA-PDT followed by glycolysis inhibition has been shown to successfully treat equine sarcoids up to 5 mm thick with a 93% response rate (*n*=27) after 1 month, compared with a 14% response rate using ALA-PDT only (*n*=7). Treated sarcoids became scabby with desquamation for 2-4 weeks before healing (Golding et al., 2017) (Fig. 3).

Prostate cancer

In humans definitive management of early stage prostate cancer with either surgery or ionizing radiation therapy is associated with significant associated morbidities due to the proximity of normal structures such as nerves, bladder and rectum. By contrast, PDT has the potential to selectively treat the prostate while sparing the surrounding normal tissues because light can be delivered to the entire prostate gland using interstitial cylindrically diffusing optical fibres. Prostate cancer is therefore an attractive target for PDT (Agostinis et al., 2011, Ahmed et al, 2012).

Vascular-targeted PDT using Padeliporfin mediated PDT and a short drug-to-light interval was shown to carry minimal toxicity in a phase I trial, of prostatic carcinoma patients (*n* = 24) with local failure following radiotherapy (Weersink et al., 2005; Trachtenberg et al., 2007). In a follow-up phase II study, patients were treated with increasing light doses. At 6 months all patients where >60% of the prostate was determined to be avascular by post-PDT magnetic resonance imaging, had negative biopsies, however, 2 patients (of 28) developed urethrorectal fisulae (Trachtenberg et al., 2008). Following refinement of the technique, a recent phase III randomised controlled study of padeliporfin vascular-targeted PDT (versus active surveillance) has shown this to be a safe and effective treatment for low risk localized prostate cancer (Azzouzi et al., 2017).

The normal canine prostate has served as a useful preclinical model for evaluating responses to PDT in vivo, since its size and general anatomical structure are similar to those of the human prostate (Waters and Bostwick, 1997). An experimental study was conducted assessing padeliporfin PDT on canine prostate pre-treated with ionizing radiation. All dogs presented normal spontaneous urination upon recovery from the procedure, with no signs of incontinence or significant macroscopic hematuria (Huang et al., 2004).Vascular-targeted photodynamic therapy with WST11 (TOOKAD Soluble) has been investigated in a dog model of benign prostatic hyperplasia and was uneventful in all except one dog, which experienced urinary retention. Prostatic urethral width increased as early as 6 weeks after treatment, while prostatic volume decreased, reaching 25% by 18 to 26 weeks, this response lasted up to 1 year (Chevalier et al., 2013). Unfortunately canine prostatic carcinoma is not usually detected until symptomatic at which point the disease is in late stage, often with metastatic disease, so it is unlikely that PDT would be beneficial in such patients.

Bladder cancer

Photodiagnosis is used in management of human bladder cancers (Mowatt et al, 2011), and bladder cancer is also a potential target for PDT. Human bladder cancers are often superficial and multifocal and can be assessed and debulked endoscopically. Furthermore, the geometry of the bladder allows for homogeneous light delivery via diffusing fibres. In general, early response rates (2 to 3 months) to PDT have been about 50% to 80% of patients with longer-term (1 to 2 years) durable responses in 20% to 60% of patients. It should be noted that many of the patients treated in these studies had recurrent disease that developed after standard therapies such as Bacillus Calmette-Guerin (BCG) (Agostinis et al., 2011). Treatment of superficial bladder cancer with PDT is generally well tolerated, with dysuria, hematuria, and skin photosensitivity being the most common acute toxicities. Bladder wall fibrosis/diminished bladder capacity can be a problem in some patients (Prout et al., 1987; Uchibayashi et al., 1995). Studies of locally applied (intravesical) ALA demonstrate that comparable complete response rates of 52-60% at 2-3 years can be achieved for patients with treatment refractory bladder carcinoma *in situ* without the prolonged skin photosensitivity experienced using systemic Photofrin (Berger et al., 2003; Waidelich et al., 2003).

Despite these promising results, PDT for bladder cancer remains largely investigational with limited use (Agostinis et al., 2011).

Canine transitional cell carcinoma (TCC) is most commonly located in the trigone region of the bladder precluding complete surgical resection and palliative medical management is often the only treatment available (Fulkerson and Knapp, 2015). PDT could represent a promising option for dogs with TCC. However, canine TCC is often diagnosed late and is more invasive than human bladder cancers, making comparisons with human studies difficult (Fulkerson and Knapp, 2015). In vitro-studies have shown, that ALA-PDT destroys canine TCC cells (Ridgway and Lucroy, 2003). When studied in vivo, 70% of dogs vomited after oral administration of ALA, but this did not appear to have a negative impact on pharmacokinetics and the active metabolite (PpIX) was shown to accumulate in the bladder mucosa, compared to the muscularis and serosa. Five dogs with TCC of the urinary bladder treated with ALA-PDT and a laser fibre delivery system, showed transient improvement of clinical symptoms with tumour progression free intervals ranging from 4 to 34 weeks (Lucroy et al., 2003a,b). The application of PDT for canine TCC clearly warrants further investigation.

Brain tumours / glioma

Experimental and clinical studies have demonstrated that PDT can complement current standard therapies (surgical resection, radiation therapy and chemotherapy) in the treatment of brain tumours (Muller and Wilson, 1995, 1996). PDT may be particularly useful as an adjunct to surgery as it can non-invasively target tumour cells infiltrating normal brain. Initial trials provided encouraging results using various formulations of hematoporphyrin derivatives (HPD, Photofrin), ALA as well as mTHPC with light sources including lamps, dye lasers and diode lasers (Agostinis et al., 2011). One of the main indications for ALA in management of glioma is in fluorescence guided surgery (FGS). ALA based FGS has been shown to provide longer survival times than conventional surgery in patients with suspected malignant gliomas (n=322), 16.7 versus 11.8 months respectively (Stummer et al., 2006).

In a canine glioma model, dogs were given 0.75 mg/kg Photofrin-II intravenously, followed 24 h later by PDT, delivered using a fiberoptic catheter directly to the tumour via a burr hole in the skull (Whelan et al., 1993). This destroyed the tumour without significant brain-stem injury.

The new classes of PSs, the better understanding of dosimetry and further improvements in technology may significantly change the currently achieved clinical outcome for glioma and other brain tumours both in human and veterinary patients. Pre-clinical data indicating that protracted light delivery may increase the therapeutic index of PDT in the brain combined with newer technologies such as implantable, LED-based light delivery systems could lead to significant improvements in treatment outcomes (Kostron, 2010).

Future perspectives

Photodynamic therapy offers great potential due to its selective targeting of tumour cells and minimal normal tissue toxicity. Several innovative strategies have been used to improve PS penetration into tumour cells, including: using an electric current to draw PS deeper into the skin (Lopez et al., 2003), intratumoural PS injection (Hage et al., 2007; Rodríguez-Prieto et al., 2012) and pretreatment with chemical penetration enhancers (Malik et al., 1995; De Rosa et al., 2000; Golding et al., 2017), liposomal formulations and nanoemulsions (Buchholz et al., 2005, 2007). The efficacy of PDT may also be improved by overcoming the antioxidant defences of cancer cells. Antioxidant defences that remove excess ROS are upregulated in many cancers (Tracootham et al. 2009), undermining the full potential of PDT. Combination of glycolysis inhibitors with PDT has been shown to deplete cellular antioxidants and significantly improve PDT cytotoxicity against human cancer cells in vitro (Golding et al., 2013) and this combination has proved effective in treatment of equine sarcoids (Golding et al 2017). Other ways in which efficacy of PDT may be improved clinically include: Metronomic PDT (mPDT) to delivery both the drug and light at very low dose rates over an extended period (hours-days) (Lilge et al., 2000), and through use of nanoparticles for PS delivery (Bechet et al., 2008). If the potential for use of PDT in veterinary medicine could be realized this could make a significant contribution to the overall development of the technique.

Conclusions

PDT is a safe and effective therapy for many cancers and pre-cancers that can be accessed externally or endoscopically. Small, localised lesions can achieve long-term clearance with negligible scarring or damage to adjacent structures.

The science of PDT has seen enormous progress within the past 30 years. For instance: the development of improved photosensitisers, light sources (including endoscopic delivery and daylight PDT), improved understanding of how PDT works, and an expansion of the uses of photosensitisers to allow intraoperative detection of tumour margins. Although PDT has hitherto been used as a monotherapy, the future of the technique undoubtedly lies in combining it with other drugs and approaches as part of a synergistic multimodal treatment.

Despite the scientific advances, the clinical practice of PDT is still limited to a small number of individual practitioners or centres of excellence; partly due to a vicious cycle of high photosensitiser costs due to limited demand. With pun intended, veterinary PDT needs to come out of the shadows and into the light. This will only happen if PDT becomes a standard part of the training syllabus and existing PDT practitioners provide internships for the next generation of veterinary surgeons. The referral system for PDT is also in need of improvement.

Conflict of Interest

None of the authors of this paper have a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Table 1.

Summary of characteristics and application of selected second generation photosensitizers.

Agent (synonyms)/ manufacturer	Activation wavelength (nm)	Advantages	Reported tumour applications (human unless stated)	References
Foscan (m-tetrahydroxophenyl chlorine (mTHPC), temoporphin)/ Biolitec Pharma.	525 - 660	-Short duration of skin photosensitivity (15 days) -High quantum yield for singlet oxygen -Depth of tumour necrosis (10 mm)	Pleural mesothelioma Head and neck cancers Oesophagus Prostate Pancreas Skin tumours Skin tumours (cats)	Friedberg et al., 2003. Rauschning et al., 2004; Biel et al., 2006. Lovat et al., 2005; Etienne et al. 2004. Nathan et al., 2002; Moore et al., 2006. Pereira et al., 2007. Triesscheijn et al., 2006. Buchholz et al., 2007.
Photochlor (2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide (HPPH))/ AdooQ Bioscience.	665 - 680	Extremely hydrophobic, increasing penetration into tissue	Obstructive oesophageal cancer oral squamous cell carcinomas (dogs) facial squamous cell carcinoma (cats) squamous cell carcinoma (horses)	Dougherty et al., 2000. McCaw et al., 2000. Magne et al., 1997. Giuliano et al., 2008.
TOOKAD (WST-09, padoporfin, palladium bacteriopheophorbide)/ Steba Biotech.	760	New generation photosensitiser with greater stability and short half-life	Prostate (dogs)	Nomura and Mimata, 2012. Huang et al., 2005.
Padeliporfin (TOOKAD Soluble, WST-11, palladium bacteriopheophorbide	760	Vascular-targeted PDT	Prostate Prostate (dogs)	Azzouzi et al., 2017. Chevalier et al., 2013.

monolysotaurine)/ Steba Biotech.				
Lu-Tex (Motexafin lutetium, lutetium texaphyrin/ Pharmacyclics Inc.	730	Water soluble. Selectively retained in tumour. Only 24 – 48 h skin photosensitivity	Prostate Rectal (dogs)	Patel et al., 2008. Ross et al., 2006.
Talaporfin sodium (aspartyl chlorin, Laserphyrin, Aptocine)/ Meiji Seika Pharma.	664 - 667	Retained in tumour for 50 h	Lung. Esophageal. Intranasal (dogs)	Usuda et al., 2007. Yano et al., 2017. Ishigaki et al., 2017.
ALA (5-aminolevulinic acid)/ various. **Methyl-ALA** (MAL, Metvix)/ Galderma. **Hexyl-ALA** (HAL Hexvix)/ Ipsen.	Pro-drugs. Each metabolized to protoporphyrin IX (414, 635)	Short loading 3 h; short skin photosensitivity 12 h Epithelial penetration improves in sequence ALA>MAL>HAL	ALA: at least 11 different human tumours. Equine sarcoids MAL: basal cell carcinoma. Equine sarcoids. HAL: prostate photodynamic detection. Prostate (dogs)	Nokes et al., 2013. Golding et al., 2017. Morton et al., 2008, 2013. Kemp-Symonds, 2012, Golding et al., 2017. Furre et al., 2005. L'Eplattenier et al., 2008.
Verteporfin (Visudyne)/ Novartis	689 - 693	Binds low density lipoprotein receptors on abnormal blood vessels and tumours	Wet macular degeneration Esophagus (dogs) Squamous cell carcinoma (horses)	Scott and Goa, 2000. Panjehpour et al., 2002. Giuliano et al., 2014.

Table 2.

Clinical Reports of photodynamic therapy (PDT) for superficial squamous cell carcinoma (SCC) or SCC *in situ* in cats

Cases / tumour location	**PDT agent**	**PDT method**	**Response rate / outcome / side effects**	**Reference**
51 cats Cutaneous SCC facial skin	HPPH-23 Pyropheophorbid-alpha-hexyl-ether	Intravenous administration Argon-pumped dye laser	Overall 61% response rate at 1 year. 100% T1a tumours, 56% T1b and18% T2b. No toxicity, but some morbidity.	Magne et al., 1997
4 dogs and 4 cats Superficial carcinoma	HPPH	Intravenous administration LED (100 J/cm^2, 33 min)	8/9 CR >50% PFS > 68 weeks. No cutaneous photosensitivity	Reeds et al., 2004
13 lesions / cats 10 nasal planum, 2 pinna 1 eyelid	ALA (Cream)	Topical application LED 635 nm 12 J/cm^2	85% CR rate But with 64% local recurrence, median 21 weeks. Cats attempt to scratch lesion after treatment. Local analgesia required.	Stell et al., 2001
18 cats with 20 cutaneous SCC	Liposomal formulation of Foscan (m-THPC)	Intravenous administration 625 nm diode laser	100% CR rate Overall 1 year control rate 75% 20% recurrence, 172 days. Mild erythema/ edema in 15% of cats.	Buchholz et al, 2007
55 cats Superficial SCC nasal planum	ALA (Cream)	Topical application LED 635 nm 12 J/cm^2	85% CR rate, 11% PR rate But with 51% recurrence; median 157 days. Transient, mild, local adverse effects.	Bexfield et al., 2008
12 cats Cutaneous SCC (7 pinna, 2 nasal planum)	Haematoporphyrin derivative (Photogem)	Intravenous administration LEDs (300 J/cm^2 30 min)	No response in invasive tumours or pinna. Small non-infiltrative lesions of nasal planum (n=3) showed CR/PR. One cat developed nasal oedema and died.	Ferreira et al., 2009

Abbreviations: LED (light-emitting diode), CR (complete response), PR (partial response), PFS (progression-free survival).

Figure legends

Figure 1. Fundamentals of photodynamic therapy.

A) Visible and near infra-red light spectrum showing the wavelengths (in nanometres) of maximum tissue penetration by light (above) and absorbance maxima of selected photosensitisers (below). B-D) Chemical structures of selected photosensitisers. E) Schematic of photosensitiser mechanism of action. Photosensitiser (PS) becomes activated (PS*) by light (hυ). PS* can undergo two types of reaction. In Type I reactions, biological material (BM) interacts directly with PS* forming ion radicals of both species ($PS^{-\cdot}$ and $BM^{+\cdot}$). BM radical interacts with oxygen and becomes oxidised. PS radical is either destroyed or reacts with oxygen to regenerate PS and make a superoxide anion ($O_2^{-\cdot}$) that can react with BM to oxidise it. In Type II reactions, PS* interacts with oxygen to regenerate PS and make singlet oxygen ($^1O_2$), which reacts with BM to oxidise it.

Figure 2. Feline nasal squamous cell carcinoma (SCC)

A) An early SCC on the right nasal planum in a Domestic Short-haired cat. B) Application of photodynamic therapy (PDT) using a high intensity light-emitting diode (LED). C) Complete resolution of the lesion at 6 weeks, with minimal scar formation.

Figure 3. Treatment of equine sarcoids.

A) Painting 5-aminolevulinic acid (ALA) onto sarcoid. B) Application of photodynamic therapy (PDT). C) Appearance of sarcoid at time of PDT treatment. D) Appearance of sarcoid 1 month after PDT.