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TOPIC PAPER

Photodynamic therapy for focal ablation of the prostate

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Abstract Although in early stages of clinical development, photodynamic therapy (PDT) shows promise in delivering focal treatment of both primary and post-radiotherapy prostate cancer. This article will review the mechanism of action of PDT, previous research using PDT for treating prostate cancer including the development of newer vascular-acting photosensitizers, and the potential advantages and disadvantages of PDT in delivering focal therapy.

Keywords Prostate cancer · Focal treatment · Photodynamic therapy

Introduction

Photodynamic therapy (PDT) involves the activation of a photosensitizer by a specific wavelength of light in the presence of oxygen to create cell damage and tissue necrosis.

PDT has the potential to deliver focal therapy for organ confined prostate cancer. This article will discuss the biological mechanism by which PDT exerts its effect, the types of photosensitizer available, the history of the development, the technique of delivering PDT to the prostate and finally the attributes of this ablative modality which may make it appropriate for the delivery of focal therapy for prostate cancer.

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The mechanism of action of photodynamic therapy

As introduced above, PDT uses a combination of three elements: photosensitising drug, light and oxygen. The photosensitizing drug is activated by a specific wavelength of light in the presence of oxygen leading to the production of reactive oxygen species, which are ultimately responsible for localised tissue necrosis.

A photosensitizer is administered (orally or intravenously) in a stable inactive form (ground state). When it is exposed to light of a certain wavelength the photosensitizer reaches a higher unstable energy state (singlet state). In this unstable form the activated photosensitizer releases energy by emitting heat, light or converting to an intermediate energy state (triplet state) prior to returning to a stable ground state.

The photosensitizer in its triplet (intermediate) state can produce superoxide and hydroxyl radicals (through a Type 1 reaction) or convert molecular tissue oxygen to form singlet oxygen (Type 2 reaction).

Singlet oxygen, hydroxyl and superoxide radicals, can all cause cell damage and cell death (Fig. 1). Drug, light and oxygen must all exceed a certain threshold for a PDT effect to occur in any unit volume.

Types of photosensitizers

Photosensitizers used in PDT can be broadly classified into tissue-activated or vascular-activated photosensitizers. The tissue-activated agents require hours to days to achieve therapeutic concentrations within tissues, with activation of the drug by laser light when the drug is at its optimal concentration in the tissue to be treated. This delay between drug administration and light activation (the drug–light interval) is therefore hours to days for tissue-activated

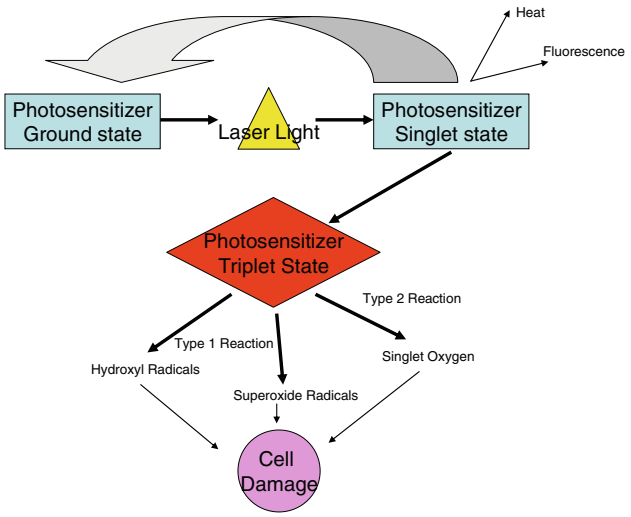

Fig. 1 Photodynamic therapy mechanism

photosensitizers. These agents also accumulate in other tissues, such as the skin and eyes, and can be activated within those organs for some time following administration. For some photosensitizers, this can be up to 6 weeks, with light protection of the skin and eyes being required.

Vascular-activated photosensitizers achieve peak concentrations within the vasculature within minutes and therefore have the advantage of having a short drug–light interval, often a few minutes. This allows for the administration of drug and light to occur in one clinical visit. In addition, these agents are cleared rapidly within hours so that patients can often be discharged without light protection on the day of treatment.

Use of PDT in other organs prior to use in the prostate

The initial role of PDT was for treating superficial conditions such as lupus vulgaris (painful tuberculosis skin lesions) in the nineteenth century and more recently skin cancer. It has been used in the treatment of age-related macular degeneration and shown to have good effect in the late 1990s [1]. The development of optical fibres suitable for interstitial treatment allowed the delivery of light within solid organs, and the use of PDT in cancers of the head, neck [2], pancreas [3] and prostate.

The history of PDT for prostate cancer

Pre-clinical work on PDT in prostate cancer was conducted in the canine prostate [4–9], which is the closest anatomical model to the human. A number of different photosensitizers was used [tin (II) ethyl etiopurpurin dichloride, motexafin lutetium, disulfonated aluminium phthalocyanine and 5-aminolevulinic acid-induced protoporphyrin IX, *meso*-tetra-(*m*-hydroxyphenyl) chlorin]. The conclusion reached at that particular time was that *meso*-tetra-(*m*-hydroxyphenyl) chlorine (mTHPC) was the most suitable photosensitizer for clinical studies.

The first use of PDT in a clinical setting used two different tissue-based photosensitizers in two patients (one received hematoporphyrin derivative and the other porfimer sodium (Photofrin; Axcan Pharma, Mont Saint-Hilaire, Canada). The patients underwent two successive transurethral resections of the prostate) followed 6 weeks later by PDT, with light delivered into the prostatic cavity using a transurethral fibre with a spherical tip [10]. These two patients were biopsied 3 months after treatment with neither having evidence of residual disease. One of the patients died of an unrelated lung tumour 6 months post-PDT (not diagnosed prior to treatment) and further histological evaluation of his prostate at post-mortem confirmed that no residual cancer was present.

The first formal clinical trial for prostate cancer was conducted in 14 patients with localised recurrent prostate cancer after radiotherapy [11]. The photosensitizer used was the tissue-activated agent mTHPC (Foscan), which was given intravenously and activated 2–5 days later by light from a 652 nm laser. This technique used freehand transperineal insertion of treatment fibres in an open access MRI scanner. Of the 14 patients, 9 had a reduction in PSA with necrosis (volumes of 0.9–13.4 cc) on MRI and biopsy. Toxicity seen in this study included stress urinary incontinence (2/14), acute urinary retention (3/14) and recto-urethral fistula (1/14). However, the fistula occurred after a rectal biopsy was taken to assess a white patch in the rectum following treatment and may be related to this secondary procedure.

The same group then conducted a pilot study using the same photosensitizer in a primary treatment setting [12]. Six patients were treated with four of these receiving a second PDT treatment due to residual cancer being found on biopsy. The other two patients also had residual cancer but one chose active surveillance and the other radiotherapy, rather than re-do PDT. The volumes of necrosis achieved, taken as the MRI volume of tissue demonstrating lack of gadolinium contrast uptake on, varied from 1.2 to 51 cm^3. All patients in this study experienced irritative lower urinary tract symptoms for up to 2 weeks. Two men required re-catheterisation (for 9 and 19 days, respectively) for acute urinary retention and one patient developed Gram-negative sepsis requiring intravenous antibiotic treatment, a day after PDT. Erectile function worsened in just one man initially but improved again spontaneously after 5 months. Thus, mTHPC was seen as a suitable candidate photosensitizer for use in PDT of the prostate,

but research into this was not further pursued by the company producing the drug.

Subsequently, further work has been conducted using a variety of photosensitizers. Aminolevulinic acid-induced protoporphyrin IX, already used in skin and oesophageal tumours, was assessed within a trial by Zaak et al. [13]. An initial study to assess the uptake of ALA in prostate cancer cells was performed, where ALA was given orally to a patient who underwent radical prostatectomy 4 h later. Fluorescence microscopy was then performed on the prostate specimen, which revealed that ALA had been taken up in the cancer cells but not in the surrounding epithelial or stromal cells. Six patients then received ALA-mediated PDT using a single 1 cm (250 J/cm) fibre. One patient had the fibre inserted at prostatectomy, two had transperineal insertion and three had transurethral light delivery. The prostatectomy specimen showed necrosis around the light fibre. In the other patients the mean PSA decreased by 30% (transperineal fibre insertion) and 55% (transurethral fibre insertion). These men did not have contrast-enhanced MRI to evaluate the volumes of necrosis achieved.

The above studies used tissue-activated photosensitizers. Since then vascular-acting PDT agents have been developed, such as motexafin lutetium (LuTex) and the palladium bacteriopheophorbide photosensitizers padoporfin (WST-09 Tookad®) and padeliporfin (WST-11 Tookad® Soluble).

Motexafin Lutetium (MLu, LuTex) has been used in 17 men with recurrent prostate cancer following radiotherapy (8 external beam and 9 brachytherapy) within a phase I trial setting [14, 15]. There was variation in the drug–light interval used with the shortest being 3 h. Both drug and light doses were escalated in this study with post-treatment monitoring of PSA levels. PSA dropped to below baseline values in those patients receiving the greatest drug and light energy dose. Again, this study did not utilise post-PDT contrast-enhanced imaging to evaluate the necrosis volumes so an objective measure of ablative ability was not possible. Many patients experienced grade 1 urinary toxicity with grade 2 urinary toxicity occurring in one man.

The palladium pheophorbide photosensitizers, padoporfin (WST-09 Tookad®) and padeliporfin (WST-11 Tookad® Soluble), are under investigation for their use in prostate cancer. The first trial using WST-09 was conducted in 24 men with recurrent prostate cancer after radiotherapy [16–18]. Initially, the drug dose was escalated (0.1, 0.25, 0.5, 1.0 and 2.00 mg/kg) in 12 patients (3 patients allocated to each drug dose) and then the light dose was escalated (using the 2 mg/kg drug dose) in another 12 men (3 at 100 J/cm, 3 at 230 J/cm and 6 at 360 J/cm). The trial established that a minimum light dose of 23 J/cm^2 in at least 90% or more of the targeted prostate volume was needed to cause necrosis (as seen on post-treatment contrast-enhanced MRI). Patients were also biopsied at 6 months post-treatment with a finding that 60% of those who received the minimum threshold light dose at 2 mg/kg drug dose had no residual disease on biopsy. Two patients in this trial developed recto-urethral fistulae, with one healing spontaneously and the other still causing intermittent problems 6 months post-treatment. Some men who had low drug and light doses in the early part of the study were re-treated with no evidence of cumulative toxicity.

Padoporfin (WST-09) was then used in primary prostate cancer [19]. This was conducted initially within a dose-escalation trial. These results are yet to be published but showed good volumes of necrosis on post-treatment MRI. No recto-urethral fistulae were observed, but intra-operative hypotension was a problem, with two patients having cardiovascular events and some subclinical hepatotoxicity [19].

Due to these problems with systemic toxicity, a new water soluble version of the drug called padeliporfin (WST-11 Tookad® Soluble) has been developed and used in 40 men in a phase I/II multi-centre trial, with good volumes of necrosis achieved (whole gland, hemi-gland and focal ablations) [20]. A further multi-centre trial is being conducted in the US with a second multi-centre European trial also currently being conducted. Recent experience using WST-11 (Tookad® Soluble) mediated PDT for localised prostate cancer has shown encouraging initial results with the ability to create discrete focal and hemi-gland ablations within the prostate. In addition it appears that extra-prostatic necrosis laterally around the prostate can be achieved without clinical sequelae for the patient. This may allow focal ablation of tumours abutting prostate capsule with an appropriate oncological margin of extra-prostatic treatment to ensure that all the cancer is treated.

For a summary of types of photosensitizer clinically trialled for prostate cancer see Table 1.

Current limitations of PDT in focal treatment of prostate cancer

Photodynamic therapy holds promise as a technology capable of focally ablating prostate tissue. However, it is important to highlight areas of improvement needed in order to make this a widely accessible tool.

First, treatment planning is currently based on pre-treatment biopsy and MRI information. The positioning of treatment fibres is thus planned on MR images, whilst the treatment is carried out using ultrasound imaging. The orientation is therefore different as well as the prostate

Table 1 Photosensitizers used in clinical PDT for prostate cancer

Type of photosensitizer	Photosensitizer	Mode of administration	Drug–light interval	Studies
Tissue based	Haematoporphyrin derivative	IV	48 h	Windhal et al. [10]
	Porfimer sodium (Photofrin)	IV	72 h	Windhal et al. [10]
	mTHPC (Temoporfin)	IV	3 days	Nathan et al. [11], Moore et al. [12]
	5-ALA	ORAL	4 h	Zaak et al. [13]
Vascular acting	Motexafin Lutetium (LuTex)	IV	3, 6 or 24 h	Verigos et al. [14], Patel et al. [15]
	Padoporfin (Tookad® WST-09)	IV	10 min	Trachtenberg et al. [16], Haider et al. [17], Trachtenberg et al. [18], Abstract: Pendse et al. [19]
	Padeliporfin (Tookad® Soluble WST-11)	IV	10 min	Abstract: Arumainayagam et al. [20]

shape, which can be deformed to varying degrees due to pressure of the transrectal probe. This in addition to gland swelling with needle insertion means the dimensions of the prostate on MRI and at the time of treatment are not the same. This could be overcome with direct ultrasound planning, MRI-ultrasound registration software or by delivering treatment within an open-core MR magnet with MR compatible equipment.

Treatment planning options in the future may involve one of a number of different approaches. For some time it has been assumed that the delivery of light for PDT in a solid organ will require the use of real-time feedback of at least one of drug, light or oxygen levels, if no specific surrogate to predict treatment effect can be found. A system to do this for prostate PDT is being developed for use with mTHPC PDT [21].

However, it is feasible that for a given drug dose and light dose per unit, a 'rules-based' approach may be appropriate. A rules-based approach would require specific rules for the placement of fibres, for example, with a certain fibre density (in cm per cc of prostate), or specific limits at different prostate boundaries e.g., 6 mm between a light delivery fibre and the rectal wall. Work is ongoing to evaluate this approach in men receiving palladium bacteriopheophorbide PDT.

At present there is no current real-time feedback of treatment effect during delivery of PDT to the prostate, although research is being conducted into monitoring the changing optical characteristics within the prostate, drug concentrations and oxygen levels within the gland [22]. Such technology if proven to work, may allow the operator to vary light dose during treatment to create more accurate focal treatments and reduce the risk of toxicity, by minimising light delivery to urethra, rectum and urinary sphincter. Intra-operative contrast-enhanced ultrasound may also play a role in this but by its very nature is not exactly real-time [23].

Advantages of PDT as a focal therapy modality

Photodynamic therapy may have some distinct advantages in its ability to deliver focal treatment of prostate cancer.

The technique of needle placement within the gland using a brachytherapy template grid is relatively straightforward.

Given that needle (and hence laser fibre) positioning is transperineal it allows treatment of anterior zones of large prostates that would otherwise be inaccessible by other certain modalities such as high-intensity focussed ultrasound (HIFU). However, this in some patients may be limited by pubic arch anatomy precluding needle insertion to anterior parts of the gland.

Manipulation of drug and light dosing can result in varied volumes of ablation. Thus, for a given drug dose the energy per centimetre of fibre can be increased to achieve a greater treatment volume. This would result in needing fewer treatment fibres for any given ablation, with resultant shorter procedure times and reduced trauma to the perineum.

There is also the potential to give fractionated light dosing with intermittent dark periods. This may allow drug and oxygen levels to recover in the target tissue, with resultant increase in the PDT effect for a given total light dose [24]. This has only been observed in experimental models, such as the rat colon tumour and non-tumour tissue with 5-ALA-mediated PDT.

There has been a long running debate about whether photosensitizers are cancer-selective or not, with ALA accumulating in cancer, but less evidence for this with other agents. The selectivity of PDT may be improved by attaching the photosensitizer to an antibody which targets the tumour [25]. There is some evidence that using monoclonal antibody linkage may be better suited to hydrophilic photosensitizers rather than hydrophobic ones [26]. Linking the photosensitizer to a monoclonal antibody

against prostate-specific membrane antigen is a possible way to improve its targeting. Another way of achieving selectivity using monoclonal antibody linkage is by utilising the over-expression of vascular endothelial growth factor (VEGF) in tumours, and using a photosensitizer linked to a monoclonal antibody against VEGF. This has been investigated for age-related macular degeneration using the rat model [27].

The use of monoclonal antibody linkage may be limited by reduced photosensitivity of the combined photosensitizer–antibody complex, compared to the free photosensitizer. Prostate tumours may have different antibody expression, both within the same lesion and between different lesions in the same gland, thus resulting in only partial treatment if a monoclonal antibody linked agent is used.

Another method of achieving selectivity is by delivering the photosensitizer into the tumour cell as opposed to only on the cell surface or the vasculature alone. This could be achieved by linking the photosensitizer to serum proteins (e.g., albumin, transferrin), to allow the photosensitizer to be taken up into the cell and its internal structures. Receptor-mediated endocytosis is the mechanism by which the photosensitizer can be taken into cells, which can be made prostate tumour selective by linking the photosensitizer to a molecule that will bind to a specific receptor that is over-expressed in prostate cancer cells.

There is some evidence in the canine model that at doses that treat glandular prostatic tissue PDT has less effect on collagen [8]. Thus, with appropriate treatment dosing and planning, PDT may have the potential to ablate prostate cancer and leave the collagenous structure of the prostate intact, potentially improving the ability to preserve structures such as the urethra and urinary sphincter.

With the development and use of vascular-activated photosensitizers, which are eliminated from the body within hours of administration and have extremely short drug–light intervals, PDT can be delivered in an ambulatory setting. This is an ideal attribute of any focal therapy treatment.

Experience, in a very small group of men who have had small volume PDT within a dose-escalation study, and that had repeat treatment at a later stage in the study, has so far suggested that PDT can be repeated for a second time without any cumulative toxicity. This is important given that prostate tissue left after focal treatment can again be ablated with PDT should residual disease or recurrent disease be identified. PDT may also be used to deliver focal salvage treatment for recurrent disease after radiotherapy.

Summary

Photodynamic therapy has the potential to be used in delivering focal treatment of prostate cancer. Recent clinical trials using vascular targeted PDT has shown it to be safe, feasible, potentially repeatable and suitable for delivery in an ambulatory care setting.

With advances in molecular targeting, PDT has the potential to be selective for tumour and further minimise toxicity to surrounding non-cancerous tissue. Light and drug-dose manipulation, combined with treatment fibre positioning, can allow the creation of accurate discrete necrotic lesions within all parts of the prostate.

Although in the early stages of development compared to other current ablative modalities (such as HIFU and cryotherapy), photodynamic therapy has the ideal characteristics required of any ablative technology for focally treating prostate cancer, and should be further explored in the setting of clinical trials.

Conflict of interest statement Nimalan Arumainayagam has received educational travel allowances from Steba Biotech SA. Caroline Moore, Hashim Ahmed and Mark Emberton are consultants to Steba Biotech SA.

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