Photodynamic therapy for prostate cancer: One urologist's perspective

Steven H. Selman MD*

Department of Urology, Medical University of Ohio, 3065 Arlington Ave., Toledo, OH 43614, United States

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Summary   Photodynamic therapy (PDT) has slowly found its place in the treatment of human disease. Currently, photodynamic therapy is being explored as a treatment option for localized prostate cancer. PDT for the treatment of prostate cancer will require ablation of both malignant and non-malignant glandular epithelium. Ablation of both malignant and normal epithelium adds a new treatment dimension since traditionally PDT has not targeted normal epithelial tissue. PDT for prostate cancer as currently envisioned will present challenges in terms of in situ monitoring of light, drug concentration, p_{O_2} levels and biologic endpoints. The introduction of vascular-targeted photosensitizers fundamentally alters the traditional axioms for successful PDT treatment by obviating the need for ''selective'' tumor localization. Should clinical trials demonstrate the utility of this approach, patients with organ-confined disease will benefit.

Introduction

Figge et al. described the propensity of certain metalloporphyrins to localize in rapidly dividing tissues [10]. Over the ensuing decades, there has been growing interest in applying this observation to the treatment of human disease. In the 1960s Lipson and Baldes described a derivative of hematoporphyrin shown to have potential for the localization in certain intraepithelial neoplasms [22]. Dougherty et al. combined the use of this compound with laser light forming the basis of the current era of photodiagnosis and what was eventually termed photodynamic therapy (PDT) [9]. Urologic applications of this technology were early appreciated. To

wit, Kelly et al. reported one of the early clinical studies using hematoporphyrin derivative (HpD) and light for the diagnosis and treatment of urinary bladder cancer [19]. By the early 1980s McPhee et al. suggested that photodynamic therapy might have a place in the treatment of carcinoma of the prostate [24]. Within the last 5—6 years clinical trials of PDT for prostate cancer have been undertaken [27,41,42]. The place of PDT in the spectrum of treatments of prostate cancer has yet to be established.

The prostate

The human prostate is a secondary sex organ located deep within the pelvis. It rests upon the urogenital diaphragm anterior to the rectum, caudal to the urinary bladder and immediately behind the pubic symphysis. Intimately associated are the paired seminal vesicals whose ducts join the aboral end of the vas deferens to form the ejaculatory ducts both of which empty into the distal prostatic urethra. The

urethra runs through the prostate serving as a conduit for urine and seminal emissions. Glandular elements make up 40% of the prostatic tissue volume while the remainder of the non-named structures is a combination of fibromuscular stroma. The cephalad end of the prostate is termed the base while the caudal end sitting on the urogenital diaphragm is the apex. Immediately adjacent to the apex of the prostate run the nervi erigentes which control erectile activity. Beyond the apex within the urogenital diaghram is the so-called external urinary sphincter part of the urinary continence mechanism. The prostate's sole function is to provide seminal fluid for procreation.

Prostate cancer

Prostate cancer is the most common neoplasm in men. This cancer arises in the acinar glands and its connecting ducts. Clinically unusual in men less than 50 years of age, the incidence of the disease increases with advancing age. There is a wide spectrum of disease from indolent cancers remaining localized to the gland for many years to rapidly growing cancers with the potential for early metastasis and death. One of the best measures of the aggressiveness is the cancer grade. The most widely used grading system is the Gleason grading system a system based on glandular architecture [11]. The examining pathologist assigns a grade [1—5] to both the major and minor patterns found on histologic examination. A score is assigned by adding the major and minor pattern grade. Scores thus range from 2 to 10 with the higher scores reflecting more aggressive cancers. The majority of prostate cancers arise in the periphery of the gland, the so-called peripheral zone [23]. For clinically localized cancer a number of treatment modalities exist. Radical prostatectomy and radiation therapy have for years been the principal modalities employed for the treatment of the disease. These treatments have evolved over the last several decades so that currently radical prostatectomy can be performed laparoscopically as a "minimally invasive" procedure while radiation therapy can be completed in one session as outpatient bachytherapy.

Other minimally invasive technologies are currently being used for the treatment of prostate cancer. Cryosurgery has been shown to successfully treat both primary cancers and those recurring after radiation therapy [28]. High intensity focused ultrasound (HIFU) is a developing technology demonstrating excellent outcomes in clinical trials to date [30].

Given the long natural history of prostate cancer, most current studies use the prostatic specific antigen (PSA) as a surrogate endpoint marker for treatment success. Prostate specific antigen is a serine protease produced by the prostatic glandular epithelium responsible for seminal liquification. Both benign and malignant glands produce PSA. After radical prostatectomy, PSA should drop to immeasurably low levels. The nadir level for success after radiation therapy is unclear but most would agree patients should achieve a sustained level below 0.5 ng/ml. New technologies will have to duplicate these levels to gain clinical acceptance. To achieve these levels both benign and malignant glandular epithelium will have to be destroyed. This will represent a new paradigm for treatment with photodynamic therapy. Thus, as originally proposed photodynamic therapy destroyed malignant tissue selectively in targeted tissues. Now the technology must ablate not only embedded neoplastic tissue but also all remaining normal glandular epithelium in order to eliminate PSA production.
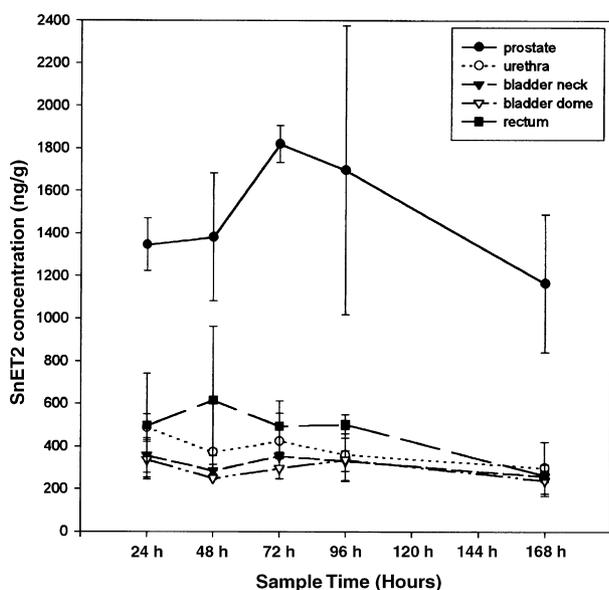
Photodynamic therapy

Daugherty and co-workers initiated the modern area of photodynamic therapy. This pioneering group used a mixture of porphyrins derived from the acidification of hematoporphyrin, hematoporphyrin derivative, as a photosensitizer. This mixture was subsequently marketed under the tradename Photofrin™. As originally hypothesized the therapeutic advantage of photodynamic therapy rested upon the preferential localization (uptake?/retention?) of systemically administered photosensitizer in neoplastic cells. This in combination with local light delivery would putatively confer a high therapeutic "ratio" to the targeted treatment site. The neoplastic cell as the target for photodynamic therapy held sway until the early 1980s a number of groups recognized that photodynamic therapy resulted in damage to tumor as well as normal microvscualture [13,34,35]. This observation raised the possibility that part of the cytotoxic effect of PDT resulted from cellular anoxia resulting from disruption of the tumor vasculature. This created somewhat of a conundrum as it was also recognized that vascular shutdown could compromise the direct cytotoxicity of PDT by limiting local oxygen supply. Henderson as well as others performed elegant studies demonstrating that varying fluence rates could profoundly affect tumor control in experimental systems by effecting local oxygen delivery [14].

Initially HpD was the sole photosensitizer used in preclinical and clinical work. HpD had as its main clinical drawback prolonged skin sensitization committing treated patients to weeks if not months of indoor confinement after administration. Subsequently, a host of photosensitizers were developed with different solubilities, pharmacokinectics and side effect profiles [2,25,40]. Many of the newer photosensitizers possessed λ_{max} in the longer visible wavelengths, wavelengths with better tissue penetration. Most of these new chlorin and porphyrin based photosensitizers had the same biologic mode of action as HpD, i.e., vascular shutdown and direct cytotoxicity. In the early 1990s Kennedy proposed an innovative approach to photodynamic therapy through the use of a new photosensitizer, aminolevulinic acid, ALA [20]. ALA is not a direct acting photosensitizer but depends on its conversion to protoporphyrin within neoplastic cells. The mode of action of this photosensitizer has not been completely delineated, as it is capable of affecting the tumor vasculature as well as direct cell toxicity [15,36]. Joining the long list of new photosensitizers is a palladium-bacteriopheophorbide, TOOKAD [31]. This is a rapidly cleared photosensitizer whose putative mode of action is purely "vascular". One of the reported advantages of this photosensitizer is its activity in areas of low tissue p_{O_2}. This is particularly germane to treatment of the prostate, as areas of low p_{O_2} have been documented in the neoplastic prostate gland [26].

Preclinical studies

Preclinical studies laid the groundwork for the current prostate cancer PDT clinical trials. McPhee and co-workers examined the feasibility of using interstitial HpD-PDT on the transplantable Dunning R3327 rodent model [24]. Long-term cures were documented. This group also published early optical studies on the prostatic tissue [1]. Subsequently, Pantelides and Whitehurst performed the first studies optical properties on human prostate finding that the extinction coefficient (μ_{eff}) (a combination of light absorption and scattering coefficients describing the light penetrating characteristics of light of a particular wavelength in targeted tissues) was $0.35 \pm 0.02\,mm^{-1}$ [29,38]. Inter-patient variation ranged from 0.28 to $0.48\,mm^{-1}$. These preclinical studies were followed by canine studies demonstrating the tissue effects of photodynamic therapy using different photosensitizers [3,4,16,21,32,33]. All of these concluded that photodynamic therapy was capable of ablating canine prostatic tissue. Additionally, the treatment seemed to spare the urethra at least in terms of mucosal regeneration.

Our group has used the photosensitizer tin etiopurpurin (SnET2) in preclinical canine prostate PDT studies. SnET2 is a lipophilic photosensitizer with an absorption peak at 665 nm. Our early pharmacokinetic studies demonstrated an increased uptake in the prostate as compared to surrounding tissues (Fig. 1). Initial studies were promising using either transurethrally launched light or interstitial placement of light fibers in terms of the effect on the prostate. Hemorrhagic necrosis was apparent when drug was delivered and tissue was treated with light 24 h later. Subsequently, we published results using both interstitial light alone and the combination of interstitial light and transurethral light. Light treatment was administered at both 24 h and 7 days after drug administration. Substantial and significant decrease in volume of the prostate and histologic destruction of tissue was documented. Other groups presented corroborating findings in similar canine studies using different photosensitizers and different times of light treatment. Of these studies, the use of TOOKAD, a palladium-bacteriopheophorbide represents a shift of the treatment paradigm for prostate tissue. This lipid soluble photosensitizer is rapidly cleared from the circulation not attaining sufficient tissue levels to create the classic photodynamic effect through direct cellular toxicity. Light is delivered within minutes of drug administration creating targeted tissue necrosis through vascular shutdown [37]. Whether ''classic'' photosensitizers create the same effect through similar timing of light administration is unclear. Studies on hypercin a newer ''classic'' photosensitizer have demonstrated that the vascular effect is the central cytotoxic mechanism [6]. Chen et al. studied both orthotopic and non-orthotopically transplanted prostate tumors and determined treating during the vascular phase of vertoporfrin administration enhances cell killing at either site [5].

Long-term (3-months) results documenting preclinical results of PDT of the canine prostate have not been widely reported. Using SnET2 we found a 61% decrease in prostate volume after SnET2 and interstitial light at 3 months. However, we found areas of viable tissue remaining within the residual prostate. Subsequent studies also demonstrated islands of viable glandular tissue surrounded by successfully ablated tissue (Fig. 2). The reasons for the failure to ablate these areas are not understood. Hahn and co-workers also found areas of viable tissue at 3 months post treatment ascribing their persistence to watershed areas of inadequate light penetration [16]. We and others are exploring real time monitoring of treatment parameters to assure adequate treatment. Monitoring of μ_{eff}, local photosensitizer concentration and with classic photosensitizers, p_{O_2} concentration may be helpful in avoiding under-treatment. Our group has been exploring integrating these parameters into a computer program for guidance in treatment [18]. Although monitoring these parameters may be helpful in avoiding under-treatment, the ''threshold effect'' for glandular ablation of human normal and prostate cancer cells with PDT has not defined. Indeed in preclinical studies using Photofrin™ considerable variation in light fluence was needed to create a biologic effect [21]. To obviate this problem, a biologic endpoint for treatment will need to be found to assure adequate treatment of targeted tissue.

Recent studies have addressed two clinically important issues in their preclinical studies: (1) the effect of previous irradiation of the prostate on the photodynamic effect and (2) the effect of PDT on peripheral nerves. It is envisioned that one of the first groups targeted for PDT will include those with local failure following radiation therapy. Since the nervi erigentes lie in close proximity to the prostatic apex, the effect of PDT on these nerves and thus sexual function is of clinical importance. To address these issues normal canine prostates were irradiated with external beam radiotherapy and then treated with TOOKAD PDT 6 months later. The photodynamic effect in the irradiated prostate was similar to that found in the nonirradiated prostate [17]. Subsequently, these same investigators found peripheral nerve conduction was impaired by ''treatment'' with TOOKAD and exposure to light. Both of these findings have obvious clinical relevance [8].

Figure 1 SnET2 concentration as a function of time after intravenous injection.
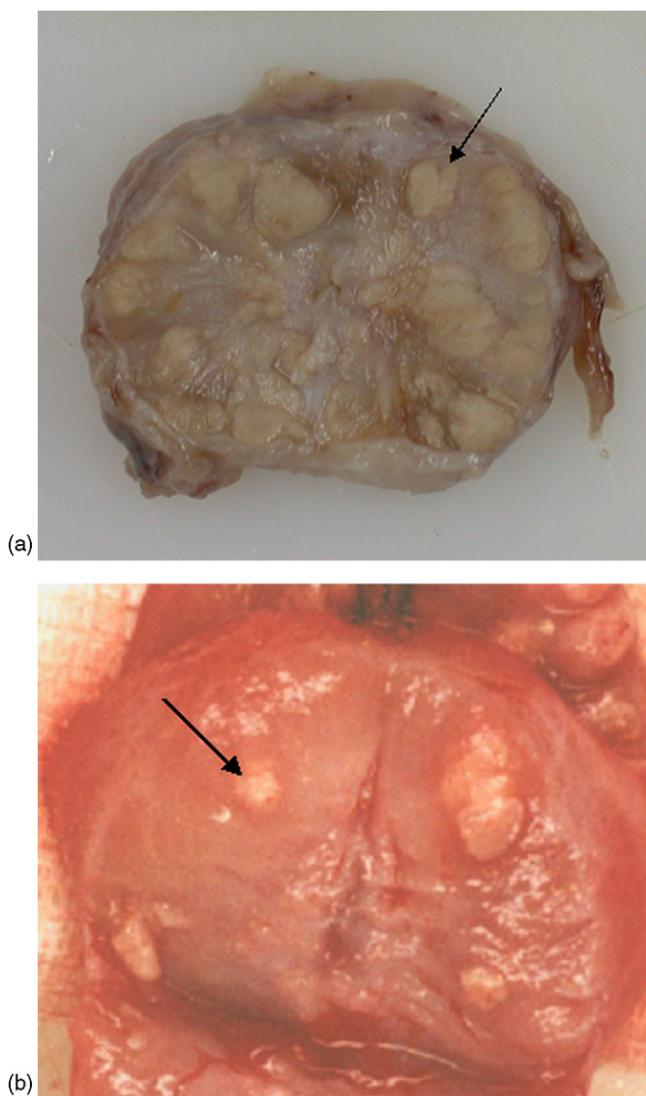
Figure 2 (a) Prostate from dog treated with 1.0 mg/kg SnET2. Prostate treated with interstitial light 24 h post photosensitizer injection, six laser diffusers (3/lobe). Prostate removed 12 weeks post PDT. Viable areas correspond to diffuser placement (arrow) and also viable areas near capsule. There was about 40—45% shrinkage of prostate. (b) Prostate 12 weeks after treatment with SnET2 and interstitial laser light. Viable areas found in both lobes (arrow).

Clinical studies

Windhal et al. were the first to use photodynamic therapy for the treatment of human prostate cancer [39]. Light was delivered transurethrally after sensitization with hematoporphyrin derivative. Two patients were treated both of whom had undergone previous transurethral resection. A drop in PSA was documented and one patient expired 6 months later of unrelated causes and no residual disease was found. No subsequent studies were reported. In 1999, Nathan reported a series of 14 patients treated with meso-tetra-(m-hydroxyphenyl)chlorin (mTHPC) as the photosensitizer [27]. Drop in PSA, MRI studies showing necrosis and post treatment biopsy were used to document

a photodynamic effect. Zaak and co-workers used 5-ALA administered orally prior to radical prostatectomy and found protoporphyrin fluorescence only in epithelial cells. Subsequently, a small group of patients were treated with interstitial PDT delivered either transurethrally, intraoperatively during radical prostatectomy or transperineally. The intraoperatively treated prostate showed necrosis within the tissue while the others showed an average decrease of 55% in PSA from the preoperative value [41]. Zhu and co-workers are currently involved in a clinical trial using Texaphyrin™. Clinical outcomes have not been reported but human studies on intra prostatic photosensitizer concentration and local μ_{eff} have been published. Geographic variations in μ_{eff} and drug concentration were documented [42]. μ_{eff} also varied during treatment, a finding reported by Chen et al. in their preclinical canine prostate studies [7]. Zhu and group concluded from these studies that a method of real time monitoring of changes in optical properties will be needed as a step to complete ablation. Studies on the use of TOOKAD are currently in progress. It is unclear whether vascular acting drugs can result in total prostate ablation while preserving normal urinary function.

From the clinical prospective a clear endpoint for treatment would be desirable. For a vascular drug, complete ischemia of the target organ would signal completion of therapy. However, the time course of ischemic changes may not be immediate and thus monitoring of blood flow during treatment might not prove adequate. Real time MRI may be useful in determining monitoring treatment [12].

Conclusion

Photodynamic therapy has slowly found its place in the treatment of human disease. The use of photodynamic therapy for the treatment of prostate cancer will require that all the glandular tissue (both normal and malignant) be ablated for success. The introduction of a photosenstizer acting only on the vasculature represents a shift in PDT treatment paradigm in that the target for killing is not the tumor cell directly but rather its nutrient blood vessels. Whether this approach to treatment proves successful has yet to be determined.

For success in the treatment of prostate cancer, treatment will most likely require real time monitoring of light, p_{O_2}/blood flow and photosensitizer concentration. Developing the systems to do this will be challenging but if accomplished rewarding for our patients.

Acknowledgements

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