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REVIEW

Vascular targeted photochemotherapy using padoporfin and padeliporfin as a method of the focal treatment of localised prostate cancer - clinician's insight

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Abstract

Vascular targeted photochemotherapy (VTP) holds promise as a novel strategy of the focal treatment of localised prostate cancer (LPCa). It is convenient to perform, minimally invasive and can be conduct in ambulatory conditions. In this review, methodologic aspects of padoporfin- and padeliporfin-mediated VTP and its clinical application in focal treatment of LPCa as well as future perspective of this method were presented. Physicochemical and pharmacokinetic parameters of padoporphin and padeliporfin using as VTP photosensitizers were described, as well as methodologic question of radiation delivery and dosimetry, and oxygen monitoring in cancer tissue in context of VTP safety and efficiency of LPCa focal therapy were discussed. The results of clinical trials concerning application of padoporfin- and padeliporfin-mediated VTP in LPCa were also presented. The future of VTP is development of protocols, founded on the real-time feedback and rules-based approach to make this strategy a standard procedure in LPCa treatment. To evaluate clinical potential of this procedure, a cost-effectiveness analysis is also necessary.

Key words: Localised prostate cancer; Focal therapy; Vascular-targeted photochemotherapy; Methodology; Clinical trials

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Core tip: Vascular targeted photochemotherapy (VTP) represents new paradigm in focal therapy of prostate cancer (PCa). Physicochemical, pharmacodynamic and pharmacokinetic properties of padoporfin and padeliporfin, which are palladium derivatives of bacteriochlorin, make them suitable photosensitizers for VTP. Good visualisation of tumours and selective targeting of tumour lesion are mandatory for VTP to be efficient. Results of clinical trials confirm safety and efficiency of VTP in treatment of PCa. New protocols are necessary to make VTP standard method of PCa therapy.

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INTRODUCTION

Prostate cancer (PCa) is the fourth most prevalent cancer in the World and the second most frequently diagnosed cancer in men. In 2012, this cancer was the fifth dominant cause of cancer death in men, even though a measurement of prostate specific antigen (PSA) levels following biopsy allows to discover prostate cancers at early stages, suitable to therapy[1,2].

In conventional therapy of PCa, the target of treatment is an entire organ seized by malignant lesions, contrary to many other tumours, such as ovarian, cervical or colorectal cancer[3]. The currently available treatment modalities for localised PCa (LPCa) are radical therapy (RT) and active surveillance. RT consists in ablation of entire prostate gland[3-6] while active surveillance includes monitoring of serum PSA concentration and repeat prostate biopsies to select patients for curative therapy[6-8]. Strategies of RT, including prostatectomy, external beam radiotherapy and brachytherapy, can result in substantial genitourinary and rectal adverse effects, that, as a consequence, damage surrounding tissues and deteriorate patients quality of life[4,9-11], whereas active surveillance presents a considerable risk of cancer progression, metastases, and patients mortality[6,12-14]. There is no difference of long-term PCa mortality (< 3%) after robotic prostatectomy comparing to that observed during 12 and more years of active surveillance[15]. Moreover, frequent medical exams during active surveillance may create adverse effects and deteriorate patient quality of life[6]. This situation gives an impetus to search new options of PCa treatment. In the last few years, the interest in focal therapy of localised PCa has increased[16].

Focal therapy is based on the conception of LPCa treatment by destruction of only cancerous lesions localised in prostate gland to spare remainder of this gland and, in this manner, to minimise morbidity[17-20]. In the case of multifocal tumours, only the index lesion, which is generally defined as the largest-volume lesion with the highest grade, is predictive of progression[3,21-24], although there are no maximum tumour volume over which focal therapy is recommended[19,25]. The strategies of prostate focal ablation may target directly the lesions identified as malignant (targeted ablation), a part of the gland that is known to harbour malignancy (zonal ablation), or a lobe along with ipsilateral neurovascular bundle (NVB) with preservation of contralateral and its NVB, involving ablation of urethra as natural boundary of ablation (hemiablation)[19,20].

The primary aim of focal therapy of LPCa is to reduce trauma to the cavernous nerves, resulting in less erectile dysfunction. The method which may adequately spare a sufficient component of the NVB, so that potency is preserved, is vascular targeted photochemotherapy (VTP), usually regarded as a form of the focal photodynamic therapy (PDT)[24,26,27].

PDT IN FOCAL TREATMENT OF PCa

In general, PDT is a minimally invasive treatment procedure, involving optical radiation (usually called "light"), oxygen, and radiation-sensitising dye, termed photosensitizer. The PDT action is based on light activation of photosensitizer localised in target tissue producing reactive oxygen species which destroy target cells though direct cytotoxicity, vascular shutdown and activation of an immune response[28-30].

The development of prostate PDT in particular has accelerated rapidly in past few decades[31-33]. Some clinical studies of prostate cancer PDT with use of transurethral or transperineal irradiation and many of photosensitizers or their precursors, such as haematoporphyrin derivative[34], meso-tetra-(m-hydroxyphenyl)chlorin[35,36], 5-aminolevulinic acid[37], motexafin lutetium (Lu-Tex)[38-40] or temoporfin[41], were conducted. The protocols of these studies were grounded on the conception of cellular-targeted photochemotherapy (CTP), in which photosensitizer after administration is preferentially accumulated in parenchymal cells of tumour and causes their damage through production of singlet oxygen when activated by radiation[42,43]. This strategy is characterised by a long interval between administration of photosensitizer and its activation with radiation [drug-light interval (DLI)] that makes this treatment uncomfortable for patients[27,44]. Moreover, CTP of prostate cancer may cause adverse effects related to both photosensitizer pharmacokinetics, such as prolonged photosensitivity, and treatment protocol, such as haematuria, infections, incontinence or prostate oedema[35,45]. Finally, this strategy does not preserve adjacent structures of prostate gland, such as NVB, rectum or urinary sphincter[27,45,46].

In this situation, a VTP as an alternative method of LPCa treatment has been proposed. In this treatment modality, the photosensitising agents following intravenous administration, remain only in the circulation until elimination from organism, with minimal or no extravasation[47-50]. Under these conditions, the VTP mediated oxidative stress is strictly limited to vascular compartment, leading to tumour cell death due to vascular occlusion and shutting down the tumour blood supply[47,51,52]. In VTP oxidative stress is mediated through superoxide radical anion, hydrogen peroxide, hydroxyl radicals and secondary reactive nitrogen species, such as nitrogen oxide, as opposed to conventional PDT, involving singlet oxygen production[53]. Therefore, some authors claimed that VTP represents a new paradigm in focal therapy of LPCa. The two novel

bacteriochlorins, padoporphin and padeliporphin, are used as photosensitizers in this treatment strategy[54,55].

PADOPORPHIN AND PADELIPORPHIN - PHOTOSENSITIZERS USED IN FOCAL VTP OF LPCa

Padoporfin (palladium bacteriopheophorbide; WST-09; Tookad®) is not soluble in water; its logP (Briggs' logarithm from octanol-water partition coefficient P, commonly used as a measure of molecular lipophilicity), is 1.38[55]. Preparing of water-soluble formulations of padoporfin for intravenous administration requires the use of solubilising agents such as Cremophor® in which photosensitizer undergoes aggregation upon injection but rapidly disaggregates in blood plasma[56,57]. Pharmacokinetic study using murine models showed that padoporfin in Cremophor® formulation, after bolus administration to healthy mice at a dose of 6 mg/kg[47] or to EMT-6 breast cancer-xenografted mice at a dose of 5 mg/kg[58], is eliminated in the two-step process from circulation of animals. The alpha- and beta-half lives are longer in the case of tumour-bearing mice (2 min and 1.3 h, respectively), comparing to these in the healthy animals (0.6 and 11 min, respectively)[47,58,59]. The total rate of clearance and the apparent volume distribution of padoporfin in the tumour bearing mice are estimated to be 11 mL/h and 0.9 mL respectively[58] while the maximal plasma concentration (C_{max}) is 19 mg/L, at the maximal plasma concentration time (t_{max}) of 5 min[58]. Similarly, in canine models, the maximum concentration of padoporfin in circulation after intravenous injection occurred in less than 10 min[60]. Padoporfin binds in 30% with human low level density lipoproteins (LDL) and in 50% with human high density lipoproteins (HDL) while its binding with human high density proteins (HDP), containing human serum albumins, is lower (about 15%)[61].

In contrast, padeliporfin (palladium bacteriopheophorbide monolysine taurine; WST-11; Tookad®Soluble; Stakel®) is soluble in aqueous solutions; its logP is -0.19[55,62]. After intravenous bolus injection at a dose of 6 mg/kg into healthy mice, this photosensitizer is eliminated from their circulation in one-step process, with half-life 1.65 min, apparent volume of distribution 2.12 mL and with rate of clearance 0.89 mL/min[55]. The C_{max} of padeliporfin is about 52 mg/L, at a t_{max} of 2 min. Within 5 min after injection, about 90% of administered dye is eliminated from mouse circulation, and 30 min after injection, the photosensitizer concentration in blood plasma reaches practically the background levels[47]. In order, after 20 min intravenous infusion at a dose of 10 mg/kg into healthy rats, the half-life of padeliporfin was 7.5 min[47]. Padeliporfin is characterised by minimal extravasation from vasculature and therefore remains in circulation even at high doses[47,63]. Contrary to padoporfin, padeliporfin binds primarily to HDP (about 80%) and poorly to LDL and HDL (5% and 15%, respectively)[61]. Preclinical studies in animal models showed that padeliporfin-mediated photosensitisation causes occlusion of the full tumour vasculature in a few minutes of treatment[50,54,55,64]. Thus, padeliporfin appears to have a higher therapeutic index and to be far easier to use in the VTP treatment of prostate cancer, comparing to padoporfin[27].

As padoporfin and padeliporfin in hydrophilic media present absorption maxima in the IR-A region (700-2500 nm)[55,65], therefore, for activation of these photosensitizing agents in VTP, the radiation at a wavelength of 763 nm and 753 nm, near to absorption maxima of these photosensitizer, is usually used[66,67]. The advantage of this radiation is its considerably deeper penetration into human prostate tissues (0.57 cm for λ = 763 nm) comparing to red light (about 10 mm for λ = 633 nm), usually used in conventional PDT[68,69].

In the clinical conditions, photosensitizers are usually delivered in form of infusion injected using a syringe pump through intravenous delivery line[70]. For delivery of padoporfin, which is not soluble in water, Weersink *et al*[70] used an aqueous formulation containing benzylic alcohol, ethanol, and Cremophor®, adjusted to pH 7.4. Due to the possibility of interactions between polyvinyl chloride (PVC) and Cremophor®, the syringe for injection and lines for intravenous photosensitizer delivery were PVC-free[70].

The short t_{max} of padoporfin and padeliporphin implies short DLI value (10 min for both theses dyes), as was shown in clinical studies[44,56,57,66,71,72]. This suggests that administration of drug and radiation may be conducted in one clinical visit[44]. In addition, due to the rapid clearance of these agents from circulation, which decreases a risk of delayed skin photosensitisation, the patients can often be discharged on the day of treatment, without long-term sunlight protection[44,66].

Monitoring of padoporphin and padeliporphin in serum is complicated, because, contrary to many other photosensitizers, they present extremely weak fluorescence, and therefore they cannot be monitored using standard fluorescence techniques[47]. For serum monitoring of these photosensitizing dyes, inductively coupled plasma mass spectrometry[47], graphite furnace atomic absorption at a wavelength 247.6 nm (palladium atomic absorption line)[58] or *in situ* absorption spectroscopy after serum protein ultracentrifugation[61] may be used, however, in clinical practice, the effect and not concentration of these drugs are usually monitored during VTP[62].

Selected physicochemical and pharmacokinetic properties of padoporfin and padeliporfin are presented in Table 1.

RADIATION DELIVERY AND MONITORING

For effective irradiation of the prostate gland, the fluence of radiation must be suitable to treat the whole

Table 1 Selected physicochemical and pharmacokinetic properties of padoporfin and padeliporfin

Parameter	Value	
	Padoporfin	Padeliporfin
logP (octanol-water)	1.38[55]	-0.19[55]
Apparent volume of distribution (mL)	[1]0.9[55]	[2]2.12[55]
Alfa half-life (min)	[1]1.86[58]	[2]1.65[55]
Beta half-life (h)	[1]1.3[58]	-
Total body clearance (mL/min)	[1]0.18[58]	[2]0.89[55]
Maximal plasma concentration (mg/L)	[1]19[58]	[2]52[47]
Maximal plasma concentration time (min)	[1]5[58]	[2]2[47]
Plasma LDL binding (%)	[3]30[61]	[3]5[61]
Plasma HDL binding (%)	[3]50[61]	[3]15[61]
Plasma HDP binding (%)	[3]15[61]	[3]80[61]
Standard intravenous drug dose (mg/kg)	2[66]	4[61]
Standard radiation fluence (J/cm)	200[83]	200[66]
Drug-light interval (min)	10[66]	10[66]
Standard irradiation wavelength (nm)	763[66]	753[66]

[1]Results obtained for mice with transplanted breast tumor cells after 5 mg/kg intravenous injection; [2]Results obtained for healthy mice after 6 mg/kg intravenous injection; [3]Results obtained for human protein fractions *in vitro*. LDL: Low level density lipoprotein; HDL: High density lipoprotein; HDP: High density protein.

volume of target tissue, and, at the same time, to spare surrounding organs of the prostate, whose functioning is essential for life[70]. Furthermore, penetration and distribution of radiation into prostate gland strongly depends on tissue optical absorption and scattering. In these conditions, interstitial light delivery in prostate cancer VTP has been proposed in which radiation is delivered *via* transperineal optical fibres positioned under transrectal ultrasound (TRUS) or magnetic resonance imaging (MRI) guidance, analogously to the procedure used in brachytherapy[70,73].

The number of fibres as well as characteristics of light sources and their positions depends on volume and shape of each prostate and on area of lesion. In the case of human prostate, up to six optical fibres may be necessary to ensure a full distribution of IR-A radiation throughout the prostate gland[70]. In this situation, radiation fluence is usually calculated as energy into unit of fibre length (J/cm) and not into unit of exposed surface (J/cm^2). The ratio of the total length of used fibres in cm to the planned treatment volume (PTV) of targeted prostate tissue in milliliter, is termed light density index (LDI) and plays an important role in optimisation of radiation delivery during VTP of LPCa[67,74].

The radiation fluence and position of fibres can be either planned in advance, on the basis of imaging data and knowledge of optical properties of tissues within prostate, or adjusted during the treatment, with use of dose rate standards, placed at the prostate boundary. In clinical practice, a combination of both these approaches is often used, with treatment plans to determine the prostate size and shape and with intraoperative adjustment, to estimate optimal fibre number, length, position and radiation dose. According to currently prescribed VTP regimens, interstitial irradiation should be conducted in a darkened room to prevent cutaneous photosensitisation, however, rapid elimination of padoporfin and padeliporfin from organism decreases the necessity to avoid a long-period sunlight exposure[75].

Intraperineal irradiation allows to modify radiation fluence during treatment to create more accurate focal treatments and reduce the risk of adverse effects by minimising light delivery to the urethra, rectum, and urinary sphincter. Intraoperative contrast-enhanced ultrasound or MRI method may play an important role in monitoring effects of VTP toward treated area[5,70]. Johansson *et al*[76] developed a real-time software tool for optimising time of prostate gland irradiation during interstitial VTP. This optimising is based on the continuous monitoring of radiation attenuation in the prostate tissues[76]. However, this method, applied in the steady state without measurement of absolute radiation fluence, cannot indicate variation of photosensitizer and oxygen concentration in the prostate tissue and, at the same time, may not reflect real conditions of VTP course[76]. As shown by Xu *et al*[77], both absorption and scattering coefficients can be determined within 10% for a wide range of optical properties using a quick and precise forward model. This creates the possibility that both radiation fluence and photosensitizer concentration can be determined from the combined steady state and frequency domain measurement and adjust the radiation dose adequately[78]. Irradiation can be applied simultaneously with photosensitizer administration, after ending of this administration or at the point of maximal serum concentration of photosensitizer[60]. For delivery of conformal radiation, the use of functional optical fibres may be necessary. Rendon *et al*[79,80] received some radiation isodose profile using diffusers with tailored longitudinal emission profiles.

OXYGEN MONITORING

Contrary to typical CTP, in the case of VTP the oxygen pressure (pO_2) of the blood is more important for effectiveness of this method than that in the parenchymal cells of tumour. This is advantage of VTP in treatment of prostate cancer, because areas of low pO_2 are documented in the parenchymal cells of malignant prostate gland[46,81]. Monitoring the haemodynamics *in situ* provides the relevant information on oxygen concentration in the blood. In some studies, a blood oxygen level dependent contrast MRI was used to demonstrate a correlation between decrease in blood saturation during irradiation and prostate cancer remission for padoporfin-mediated VTP[51,70]. This imaging method represents spatial and temporal changes in oxygenation, flow and volume of blood[82].

CLINICAL TRIALS

Phase I trials

Weersink *et al*[83] performed study of cutaneous photosensitivity as potential adverse effect of LCaP treatment with padoporfin VTP, as a part of phase I clinical trial

concerning application of padoporfin-mediated VTP in the therapy of prostate cancer. Padoporfin at a dose of 0.1-2 mg/kg was administered to 10 patients with LPCa and, subsequently, the prostate glands were irradiated using diode laser with radiation of 763 nm, through optical fibres placed percutaneously to deliver radiation fluence of 10-360 J/cm in each lobe of the prostate. DLI was 6-10 min, and irradiation time was 17-30 min. For testing skin photosensitivity, at 7-28 d before treatment, the minimum erythema dose in each patient was determined by exposing four square spots on the back to solar radiation simulating lamp without and with ultraviolet (UV) filter, at a fluence from 1 to 128 J/cm^2. The irradiation with full spectrum of solar-simulated radiation source did not increase skin erythema after intravenous administration of padoporfin while after removing UV region from this spectrum with optical filters, no phototoxic effects were observed when skin was exposed to light at a fluence of 128 J/cm^2, and time interval of 1-3 h after photosensitizer administration. These results suggests that cutaneous photosensitivity during padoporfin-mediated VTP of LPCa is negligible under clinical protocol[83].

Phase Ⅰ clinical trial of padoporfin-mediated VTP in 24 patients with locally recurrent PCa after external beam radiotherapy (EBRT), was conducted by Trachtenberg *et al*[56]. In this study, safety of VTP, as well as tumour response to escalating photosensitizer doses and radiation fluences were examined. Both padoporfin doses and radiation fluences at a wavelength of 763 nm were increased to the maximal values of 2 mg/kg and 360 J/cm^2, respectively. The treatment response was evaluated a week after treatment using gadolinium enhanced MRI.

The results of this study revealed strong dependence of prostate cancer response to VTP treatment on photosensitizer dose and radiation fluence. The considerable variability among patients in the response was also observed, even when drug doses and radiation fluences were the same. Only in patients receiving the highest drug/radiation dose, the sizeable necrotic zones (up to 2.2 cm diameter) in tumour tissue were observed. Avascularity regions detectible using MRI 7 d after treatment corresponded to regions of histopathological fibrosis in which no residual viable tumours were apparent. These results suggested the utility of MRI after VTP treatment as an early marker of response[56].

Phase Ⅰ/Ⅱ trials

Gertner *et al*[84] conducted the phase Ⅰ/Ⅱ two-centre clinical trial for assessment of safety, efficiency and pharmacokinetics of padoporfin-mediated VTP in patients with locally recurrent PCa after EBRT. The sensitizer was administered intravenously at a dose of 0.1-2.0 mg/kg and radiation was delivered at a fluence of 100 J/cm of laser delivery fibres. Padoporfin concentration was measured in blood and urine samples and skin photosensitivity was also evaluated. Treatment response was evaluated using measurement of serum PSA level, biopsy and gadolinium-enhanced MRI. The molecules of contrast agent, which contain gadolinium ions, are selectively captured by tumour cells to make these cells more visible in magnetic resonance image and, at the same time, to increase MRI precision and resolution in PCa diagnostics[85]. No photosensitizer adverse effects including skin photosensitivity were observed. There was linear relationship between dose and plasma concentration of padoporfin and no detectable plasma level of this photosensitizer by 2 h after irradiation was detected. No padoporfin concentration in urine at any time point during one week after treatment was observed. The lesion formation in tumour tissues on gadolinium-enhanced MRI was seen. Average depth of the effective penetration of radiation was 5.5 mm in the lesions and 3.2 mm in the selected tissue regions that revealed no MRI response. These results showed that padoporfin mediated VTP is a safe and efficient method of radiation recurrent LPCa treatment. Decrease of effective penetration of radiation in the unresponsive areas may be probably caused by fibrosis and calcification in the tissue of prostate cancer recurrent after radiation[84].

Arumainayagam *et al*[86] undertook the phase Ⅰ/Ⅱ study of drug dose and radiation fluence escalation in the padoporfin-mediated VTP, in patients previously subjected to active surveillance. For this trial, 34 men with gleason score $\leqslant$ 7 and PSA < 20 μg/L were enrolled. The patients received 2 mg/kg padoporfin in a 20 min infusion, following illumination with 763 nm radiation with use of a diode laser. The radiation fluence was increased from 100 to 300 J/cm. Under general anaesthetic, optical fibres within plastic needles were inserted into the prostate upon guidance with use of TRUS and perineal template. The procedure took 120-150 min depending on number of inserted fibres and size of prostate. The VTP-induced necrosis, as a measure of treatment efficiency, was evaluated with use of gadolinium-enhanced MRI, at a week after irradiation. The optimal radiation fluence for producing controllable ablation was 200 J/cm. In patients receiving this fluence of radiation, up to 73% necrosis of the prostate was observed, with sparing of capsule and extraprostatic tissues. The adverse effects on urinary tract were mild and transient. The irritative symptoms, persisting in many patients less than two weeks, were only recognised, whereas no incontinence episodes were reported. In one patient, hypotension caused an adverse cardiac event and a stroke. The authors supposed that observed cardiovascular adverse effects were caused by the formulation of the photosensitizer that is water insoluble and requires Cremophor® for intravenous administration. For this reason, the clinical trial has been withdrawn[86].

A prospective, multicentre, phase Ⅰ/Ⅱ study of the tolerability and safety of one-sided padeliporfin-mediated VTP in patients with LPCa was also completed. Treatment consisted of a single, 10 min, intravenous administration of padeliporfin at doses of 2, 4 or 6 mg/kg, followed by irradiation with laser at a wavelength of 753 nm and fluences of 200 or 300 J/cm. The radia-

tion was delivered for 20 min through transperineal interstitial optical fibres inserted into implant catheters and positioned with use of brachytherapy-like template under guidance of TRUS. Six positive results of biopsies in the month was indication for patient retreatment with padeliporfin-mediated VTP[87].

Azzouzi *et al*[88] conducted a pooled analysis of results obtained for 117 men from one phase Ⅰ/Ⅱ (NCT00946881) and 2 phase Ⅱ (NCT00707356, and NCT00975429) clinical trials with LPCa, PSA < 10 μg/L, and Gleason score ⩽ 7, who received padeliporfin at a dose of 4 mg/kg in 10 min intravenous infusion, following illumination with 753 nm radiation at a fluence of 200 J/cm delivered by transperineal fibres inserted in the prostate under TRUS guidance. Primary outcome was negative biopsies results in the treated lobes during six month after treatment. PSA concentration was determined at 1st, 3th, and 6th month after VTP. Magnetic resonance imaging was conducted at a week, as well as at 3, and 6 mo after irradiation. Furthermore, International Prostate Symptom Score (IPSS), International Index of Erectile Function (IIEF-5) and adverse effects were assessed at 7 d, and at 1, 3, and 6 mo after procedure. In a 6th month, the negative biopsy outcomes were observed in 68.4% of overall examined population (n = 114) and 80.6% of patients treated with hemiablation with LDI ⩾ 1 (n = 67). PSA concentration in both groups decreased by 2.0 μg/L at 6th month of trial and percent of prostate necrosis at a first week of study was 76.5% and 86.3%, respectively. Minor variations of IPSS and IIEF-5 parameters suggested an inconsiderable amelioration of urinary function and an unimportant exacerbation of sexual function. In spite of this fact, patients tolerated this procedure well, and the authors found it to be a promising method of PCa treatment[62].

Phase Ⅱ trials

Trachtenberg *et al*[57] executed phase Ⅱ case study to evaluate efficiency of padoporfin-mediated VTP as a method of ablation of the entire prostate gland in patients with recurrent LPCa after the EBRT failure. Twenty-eight patients enrolled in this trial received a padoporfin dose of 2 mg/kg and a specific radiation fluence (λ = 763 nm), established in computer-assisted treatment plan. A complete response required radiation fluences of at least 23 J/cm^2 in 90% of the prostate volume. An increased radiation fluence ameliorated the tissue response, encompassing up to 80% of the prostate in some patients. Among the 13 patients who received at least this radiation fluence, 8 had negative results of biopsy at 6 mo. Adverse effects were moderate and self-limited in most patients; two patients had recto-urethral fistulae, one of which closed spontaneously. Padoporfin-mediated VTP produced large avascular regions in the irradiated prostate, and caused complete negative-biopsy response at high radiation doses. It enables the treatment of entire prostate gland with minimal damage of surrounding tissues. The results of this study reveal clinical potential of padoporfin-mediated VTP with to treat recurrence of prostate cancer after EBRT[57].

Arumainayagam *et al*[72] achieved hemiablation in 40 patients using padeliporfin-mediated VTP with transperineally delivered radiation. Development of necrosis was assessed using MRI. Only two patients reported urinary retention as adverse effects, however patient quality of life during the treatment was not evaluated[72]. In analogous study of Azzouzi, necrosis was seen with use of MRI in 87% of the treated lobes. Concerning adverse effects, two cases of prostatitis, and single cases of haematuria, orchitis, optic neuropathy, and urethral stenosis were reported[88].

Quoraishi *et al*[74] made multicentre phase Ⅱ clinical trial to optimise conditions of padeliporfin-mediated VTP in LPCa treatment in the case of 40 patients with PSA concentration < 10 μg/L. Photosensitizer was administered intravenously at a dose of 2-6 mg/kg and radiation at a wavelength 753 nm and fluence 200 J/cm was delivered through optical fibres, embedded into prostate gland under TRUS guidance. Three treatment plans: Targeted, subtotal or hemiablation were realised upon gadolinium-enhanced MRI guidance. The results of study revealed that VTP mediated with padeliporfin with photosensitizer dose 4 mg and radiation fluence 200 J/cm with LDI = 1 is an effective and safe method of LCaP trearment. In patients treated according to this protocol, a maximal therapeutic effect (no gadolinium sequestration in 95% of PTV) was observed by MRI at a week after VTP session and a negative biopsy rate was indicated as 83% at 26 wk after VTP procedure. At the same time, average scores of IPSS and quality of life revealed statistically significant improvement comparing to baseline whereas IIEF-5 score did not significantly change. In contrast, patients receiving padeliporfin at a dose of 2 mg/kg revealed no significant therapeutic effect, while in the men receiving photosensitizer at a dose of 6 mg/kg, necrotic areas in adjacent organs were indicated, although no clinical consequences of this event were reported[74].

Eymerit-Morin *et al*[89] investigated histological changes in biopsies of 56 patients with LPCa, taken 6 mo after VTP mediated with padeliporfin infusion and low-energy laser radiation delivered to the tumour environment by optic fibres inserted through the transperineal route. In 53 patients, sharply demarcated hyaline fibrotic scars, with rare atrophic glands, in the some cases reduced to corpora amylacea surrounded by huge multinuclear macrophages, were detected. Mild chronic inflammation, hemosiderin, and coagulative necrosis were also shown. The residual cancer in a treated lobe of 17 patients, was always located outside the scar, most often close to the prostate capsule, and revealed no changes related to VTP. In contrast to radiotherapy or hormone therapy, interpretation of histological changes after padeliporfin-mediated VTP was easy. This modality caused complete ablation of carcinoma within the targeted tissue[89].

Steba Biotech[90] and Azzouzi *et al*[91] made a multi-centre, multi-arm, open-labeled, phase Ⅱ clinical trial, to estimate the optimal treatment conditions for accomplishment of prostate tumour ablation and to evaluate the therapeutic effects of VTP mediated with padeliporfin in 86 patients with LPCa. According to the treatment protocol, padeliporphin was administered intravenously at doses of 4 or 6 mg/kg and radiation at a wavelength of 753 nm and at fluence of 200 or 300 J/cm, was delivered through transperineal interstitial optical fibres. The fibres were positioned in the prostate gland under ultrasound imaging and tumour location was additionally established using MRI and transrectal biopsy. The number of fibres and the total light energy were adapted to each patient individually, based on a treatment planning proposed by treatment planning group[91]. Biopsy results, dynamic contrast-enhancement MRI at a week after treatment and analysis of the safety information revealed that 4 mg/kg padeliporfin and 200 J/cm radiation create the optimal treatment conditions for the VTP treatment of LPCa, leading to negative biopsies at 6 mo in > 80% of patients treated with this regimen. Moreover, this procedure was well tolerated by patients and showed early signs of efficiency for minimally invasive focal treatment of LPCa[90].

A prospective, multicentre, open-label, phase Ⅱ clinical trial was also completed, to establish the optimal photosensitizer concentration and radiation fluence for achievement of prostate ablation with use of padeliporfin-mediated VTP in men with early prostate cancer[92]. The efficiency criteria were histological evaluation of a 6-mo biopsy, and assessment of hypoperfusion volume using gadolinium-enhanced MRI at 7 d after treatment. Safety and health-related quality of life were also evaluated. The results of this trial were reported in the work of Moore *et al*[67]. In this trial, 40 patients suffering from low-risk prostate cancer received padeliporfin at a dose of 2, 4 or 6 mg/kg, following irradiation with 753 nm radiation at a fluence of 200 J/cm. Photosensitizer was administered intravenously in a 10 min infusion. Radiation was delivered using diffusing fibres positioned in the prostate gland upon TRUS guidance. To evaluate treatment results, MRI at 7 d after treatment was used. IPSS, IIEF-5 and adverse effects at 7 d, 1, 3 and 6 mo after VTP were also assessed. The biopsies guided with TRUS were collected at 6 mo. The three treatment plans for focal VTP therapy were applied: Whole gland ablation, hemiablation and bilateral quadrant ablation that targets a quarter of the prostate to spare the remainder of the untreated gland[20,67,92].

Maximal treatment effect (95% of the PTV) was observed by MRI at 7 d after illumination, in patients who received photosensitizer at a dose of 4 mg/kg, radiation fluence of 200 J/cm and whose LDI was higher than one. In the case of 12 men treated with these parameters, the negative biopsy rate was 83% at 6 mo, comparing to 45% determined for the subjects who received other drug doses (10 patients) or whose LDI was lower than one (16 patients). Both IPSS and IIEF-5 scores were not significantly different between baseline and 6 mo after VTP. As adverse events, only transient urinary inconveniences were reported by the patients. No cases of hypotension, which is an important problem in padoporfin-mediated VTP, were observed. These results suggest that VTP using padeliporfin at a dose of 4 mg/kg and irradiation with 753 nm radiation at a dose of 200 J/cm may be promising modality of the treatment of early prostate cancer leading in patients with LDI > 1 to necrosis 95% of the planned treatment volume and to negative biopsy rate at 6 mo of 83% men[57,67].

Phase Ⅱ/Ⅲ trials

The open-labelled, multicentre, 6-mo phase Ⅱ/Ⅲ clinical trial with an additional follow-up at 12 mo, was initiated, to establish efficiency and tolerability of the padoporfin-mediated VTP treatment of prostatic carcinoma. According to treatment protocol padoporfin was administered to patients at a dose of 2 mg/kg in the intravenous infusion, while laser radiation at a wavelength of 763 nm was delivered through optical fibres inserted through the perineum to the prostatic lobes. Patients who are eligible to participate in this trial presented with clinically diagnosed positive biopsies diagnosed after external radiotherapy or temporary brachytherapy, and with increasing PSA concentrations on three subsequent measurements after radiotherapy. This study has been terminated because of sponsor decision to develop padeliporfin as a safer and more efficient candidate for therapeutic applications[93].

During Ⅱ and Ⅲ Phase clinical trials, the standardised procedure of PCa treatment using padeliporfin-mediated VTP, was drawn up. General anaesthesia was necessary to achieve complete immobility of patients during the whole procedure and at the same time to keep safety and efficiency of treatment. The prostate and the adjacent structures were visualised by the biplane TRUS probe. For installation of optical fibres, the transparent fibre insertion catheters (FIC) were situated into the prostate transperineally through the template using the TRUS scan system, according to the treatment guidance provided by the software TOOGUIDE®. The optical fibres were calibrated to adjust the radiation power within ± 5 mW. The positions of these fibres defined a precisely targeted treatment area. With the optimal treatment conditions each centimetre of fibre induced 0.8-1 cm^3 of necrosis with more than 90% of necrosis of the targeted volume. The LDI was above one to assure favorable condition irradiation, better than in the case of hemiablation procedure. When all FICs and optical fibres were in position, the light of the room was dimmed and the patient was entirely protected from light exposure. The only exposed zone was the perineum. The infusion of photosensitizer was administered using opaque syringe and line.

Patients received padeliporfin at a dose of 4 mg/kg in a single, 10 min intravenous infusion and prostate glands were continuously irradiated through diffusing

Table 2 Vascular targeted photodynamic therapy using padoporfin and padeliporfin in the treatment of localised prostate cancer - clinical trials

Phase	No. of patients	Photosensitizer	Radiation	Ref.
I	10	Padoporfin, 0.1-2 mg/kg (0.1, 0.25, 1 and 2 mg/kg)	763 nm, 100-360 J/cm	Weersink *et al*[83]
I	24	Padoporfin, 0.1-2 mg/kg	763 nm, 100, 230 and 360 J/cm	Trachtenberg *et al*[56]
I / II	15	Padoporfin, 0.1-2 mg/kg	763 nm, 100 J/cm	Gertner *et al*[84]
I / II	34	Padoporfin, 2 mg/kg	763 nm, 100-300 J/cm	Arumainayagam *et al*[86]
I / II	30	Padeliporfin, 2, 4 and 6 mg/kg	753 nm, 200 and 300 J/cm	https://clinicaltrials.gov/ct2/show/NCT00946881[87]
II	28	Padoporfin, 2 mg/kg	763 nm, 0.1-1000 J/cm	Trachtenberg *et al*[57]
II	40	Padeliporfin, 2, 4 and 6 mg/kg	753 nm, 200 J/cm	Arumainayagam *et al*[72]
II	40	Padeliporfin, 2-6 mg/kg	753 nm, 200 J/cm	Quoraishi *et al*[74]
II	85	Padeliporfin, 4 mg/kg	753 nm, 200 J/cm	Azzouzi *et al*[88]
II	56	Padeliporfin, 4 mg/kg	753 nm, 200 J/cm	Eymerit-Morin *et al*[89]
II	86	Padeliporfin, 4 and 6 mg/kg	753 nm, 200 and 300 J/cm	https://clinicaltrials.gov/ct2/show/-NCT00975429[90]
II	117	Padeliporfin, 4 mg/kg	753 nm, 200 J/cm	Azzouzi *et al*[62]
II	40	Padeliporfin, 2, 4 and 6 mg/kg	753 nm, 200 J/cm	Moore *et al*[67]
II	40	Padeliporfin, 2, 4 and 6 mg/kg	753 nm, 200 and 300 J/cm	https://www.clinicaltrials.gov/ct2/show/NCT00707356[92]
II / III	86	Padeliporfin, 4 mg/kg	753 nm, 200 J/cm	Azzouzi *et al*[91]
II / III	16	Padoporfin, 2 mg/kg	763 nm, no information on radiation fluence	https://www.clinicaltrials.gov/ct2/show/-NCT00312442[93]
II / III	1	Padeliporfin, 4 mg/kg	753 nm, 200 J/cm	Azzouzi *et al*[94]
II / III	19	Padeliporfin, 4 and 6 mg/kg	753 nm, 200 and 300 J/cm	Lebdai *et al*[95]
III	81	Padeliporfin, 4 mg/kg	753 nm, 200 J/cm	https://clinicaltrials.gov/ct2/show/-NCT01875393[96]
III	400	Padeliporfin, 4 mg/kg	753 nm, 200 J/cm	https://clinicaltrials.gov/show/-NCT01310894[97]

optical fibres with a 753 nm radiation at a radiation dose of 200 J/cm, delivered by a multichannel diode laser. The irradiation started immediately after the end of the infusion and lasted 22 min and 15 s, to coincide with the maximal plasma concentration of padeliporphin. The total duration time of the full procedure was 1.5 to 2 h, depending on the volume of the targeted area and the number of optical fibres to be placed[68,88,94].

Lebdai *et al*[95] evaluated safety, efficiency and feasibility of salvage radical prostatectomy (RP) after padeliporfin-mediated VTP using results obtained for 19 patients from France during II phase (NCT00707356 and NCT00975429) and III phase (NCT01310894) clinical trials. The median of operation time, of hospital stay and of delay between VTP and RP were 150 min, 7 d and 17 mo, respectively. During operation, median blood loss was 150 mL, and median PSA concentrations before and after operation were 6.30 and 0.02 ng/mL, respectively. No perioperative mortality has been reported, and only 3 patients revealed complications such as pelvic hematoma, or superficial wound infection. Several patients revealed erectile dysfunctions before or after RP. Positive margins were significantly associated with bilateral VTP. Six patients underwent complementary radiotherapy. These outcomes suggest that salvage RP after VTP treatment is a safe, efficient and feasible method for treatment of locally recurrent PCa. However, to confirm this supposition, long-term studies are necessary[95].

Phase III trials

For evaluation of efficiency and safety of padeliporfin-mediated VTP in treatment of LPCa as well as for assessment of patient quality of life after this treatment, the interventional phase III clinical trial has been developed. For this study, 81 patients from Mexico, Panama and Peru have been recruited. Padeliporfin was administered at a dose of 4 mg/kg in 10 min infusion, following laser irradiation at a wavelength of 753 nm and radiation fluence of 200 J/cm, delivered transperineally through optical fibres embedded into the prostate under ultrasound imaging. The follow-up was conducted 12 mo after irradiation, assessing quality of life, urinary and erectile functions. PSA concentrations were determined at 3, 6 and 12 mo after application of VTP and clinical efficiency of this method was evaluated at 1, 3, 6 and 12 mo after its application. The results of this trial are currently completed[96].

The multicentre, randomised controlled, open label phase III clinical study to compare safety and efficiency of padeliporfin-mediated VTP with active surveillance in treatment of localised prostate cancer was also initiated. This study will include 400 patients, from which a half will be treated with active surveillance and the other half with VTP mediated with padeliporfine. The procedure will be the same as in the trial described above. This trial is not yet enrolling participants[97].

The main characteristics of described clinical trials are summarized in Table 2.

CONCLUSION

VTP holds promise as a novel strategy of the focal treatment of LPCa. This treatment modality is convenient to perform, minimally invasive and do not need long anaesthesia (usually about 2 h), therefore it can be conduct in ambulatory conditions. Intraperitoneal irradiation enables changing radiation parameters during

VTP session, to target tumour foci more precisely and to avoid the risk of adverse effects on parts of prostate which are not seized by cancer lesions as well as on tissues and organs surrounding prostate gland[5,70].

Although VTP is not yet the standard strategy for organ confined PCa, it is the therapeutic approach with the most important future potential. To make this strategy a standard element of PCa therapy, the new VTP protocols, founded on the real-time feedback and rules-based approach of treatment parameters, are necessary[44,97]. Multiparametric MRI with gadolinium contrast may be suitable for detection and characterisation of therapy progress during VTP treatment[98-101]. Intraoperative contrast enhanced high-intensity focused ultrasound may also play a role in VTP monitoring, however this imaging technique is not exactly real-time by its nature[102,103]. In order, rules-based approach would involve specific fibre density, or specific limits at different prostate boundaries[77]. As some authors indicate the low costs of photochemotherapeutic methods as their advantage over other strategies of prostate cancer therapies[17], a systematic cost-effectiveness analysis for VTP application in PCa treatment is indispensable.

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