Final Results of a Phase I/II Multicenter Trial of WST11 Vascular Targeted Photodynamic Therapy for Hemi-Ablation of the Prostate in Men with Unilateral Low Risk Prostate Cancer Performed in the United States

Samir S. Taneja,*,† James Bennett, Jonathan Coleman,† Robert Grubb, Gerald Andriole,‡ Robert E. Reiter,† Leonard Marks, Abdel-Rahmene Azzouzi and Mark Emberton†

From the Division of Urologic Oncology, Department of Urology, New York University Langone Medical Center (SST) and Departments of Urology, Memorial Sloan Kettering Cancer Center (JC), New York, New York, Emory University Hospital Midtown/Midtown Urology (JB), Atlanta, Georgia, Washington University School of Medicine (RG, GA), St. Louis, Missouri, University of California at Los Angeles School of Medicine (RER, LM), Los Angeles, California, and Centre Hospitalier Universitaire d'Angers (ARA), Angers, France, and Division of Surgery and Interventional Science, University College of London (ME), London, United Kingdom

Abbreviations and Acronyms

AE = adverse event
DCE = dynamic contrast enhanced
DLT = dose limiting toxicity
DSMB = Data and Safety Monitoring Board
FACT-P = Functional Assessment of Cancer Therapy-Prostate
I-PSS = International Prostate Symptom Score
IIEF-5 = Index of Erectile Function
LDI = light density index
mpMRI = multiparametric MRI of prostate
MRI = magnetic resonance imaging
MTD = maximum tolerated dose
PCa = prostate cancer
PSA = prostate specific antigen
VTP = vascular targeted photodynamic therapy

Purpose: Vascular targeted photodynamic therapy with WST11 (TOOKAD® Soluble) is a form of tissue ablation that may be used therapeutically for localized prostate cancer. To study dosing parameters and associated treatment effects we performed a prospective, multicenter, phase I/II trial of WST11 vascular targeted photodynamic therapy of prostate cancer.

Materials and Methods: A total of 30 men with unilateral, low volume, Gleason 3 + 3 prostate cancer were enrolled at 5 centers after local institutional review board approval. Light energy, fiber number and WST11 dose were escalated to identify optimal dosing parameters for vascular targeted photodynamic therapy hemi-ablation. Men were treated with photodynamic therapy and evaluated by posttreatment magnetic resonance imaging and biopsy. Prostate specific antigen, light dose index (defined as fiber length/desired treatment volume), toxicity and quality of life parameters were recorded.

Results: After dose escalation 21 men received optimized dosing of 4 mg/kg WST11 at 200 J energy. On posttreatment biopsy residual prostate cancer was found in the treated lobe in 10 men, the untreated lobe in 4 and both lobes in 1. At a light dose index of 1 or greater with optimal dosing in 15 men 73.3% had a negative biopsy in the treated lobe. Six men undergoing retreatment with the optimal dose and a light dose index of 1 or greater had a negative posttreatment biopsy. Minimal effects were observed on urinary and sexual function, and overall quality of life.

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* Correspondence: Division of Urologic Oncology, Department of Urology, New York University Langone Medical Center, 150 East 32nd St., Suite 200, New York, New York 10016 (telephone: 646-825-6321; FAX: 646-825-6399; e-mail: samir.taneja@nyumc.org).

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Conclusions: Hemi-ablation of the prostate with WST11 vascular targeted photodynamic therapy was well tolerated and resulted in a negative biopsy in the treated lobe in the majority of men. Dosing parameters and the light dose index appear related to tissue response as determined by magnetic resonance imaging and biopsy. These parameters may serve as the basis for further prospective studies.

Key Words: prostatic neoplasms, photochemotherapy, laser therapy, ablation techniques, WST11 compound

In recent years there has been growing interest in tissue ablative strategies for focal therapy for localized PCa.[1–3] While early results of limited clinical trials have been promising, several obstacles remain before widespread adoption.[4] In addition to a lack of long-term oncologic outcomes, short-term challenges in trial design persist, including candidate selection, method of treatment guidance, optimal energy source and appropriate end points for followup.[1,3,5] Several energy sources have been tested in the prostate, demonstrating variable outcomes in local tissue destruction and tolerability[6–8] but there are limited data on the use of treatment planning and image correlation for evaluation of tissue necrosis.[9–12]

One well studied and proven form of soft tissue ablation is photodynamic therapy, which refers to tissue destruction created by the interaction of a specific wavelength of light with a photosensitive agent.[9,13,14] Several advantages of photodynamic therapy have been recognized, including the lack of reliance on thermal energy dispersion or the heat sink effect.[15] WST11 is a recently described photodynamic agent that is retained in the vascular compartment and mediates ablation through localized generation of oxygen free radicals, resulting in vascular thrombosis and local cellular apoptosis.[16–19] We performed a prospective phase I/II multicenter trial of WST11 mediated VTP for the focal ablation of PCa.

METHODS

Study Design

This was a multicenter phase I/II, nonrandomized, open label trial performed at 5 centers in the United States (ClinicalTrials.gov Identifier NCT0094681). Following approval by local institutional review boards 30 men with serum PSA 10 ng/ml or less, clinical stage T1c/T2a, unilateral PCa demonstrated on a minimum 12-core transrectal prostate biopsy who had been offered but refused traditional therapy were enrolled in study. Men were excluded if biopsy Gleason score was greater than 3 + 3, they had greater than 50% of sampled cores positive, bilateral disease, any core with cancer length greater than 5 mm, current PCa treatment, hormonal deprivation (excluding 5α-reductase inhibitors), or supplementation within 6 months or previous transurethral resection of the prostate.

The primary objective of the study was to define the optimal drug and light dose necessary to achieve negative biopsy in the treated lobe through sequential escalation of drug dose, light fiber number and energy, and determine the safety and tolerability of WST11 mediated VTP. Secondary outcomes included quality of life, drug pharmacokinetics and pharmacodynamics.

Treatment Planning

Men included in analysis underwent mpMRI. This was centrally reviewed by an external committee to determine the necessary tissue volume to be treated to achieve hemiablation of the cancer bearing lobe, plan the number, length and position of light fibers to be used in treatment and identify obvious radiographic presence of extracapsular disease. This was not for cancer diagnosis or localization.

Treatment and Followup

Treatment consisted of unilateral hemi-ablation of the affected lobe. The procedure was performed using general anesthesia and has been previously described in detail.[10,14,15] Briefly, VTP consisted of a single 10-minute intravenous administration of the designated dose of WST11 followed immediately by a 20-minute light exposure interval. Light activation was delivered through transperineal interstitial optical fibers placed prior to IV WST11 administration under transrectal ultrasound guidance in accordance with a previously devised mpMRI based treatment plan. Laser light at 753 nm was delivered at the designated energy level using a Model 8CH-753 Mk II multichannel diode laser (V-Gen Electro Optics, Tel Aviv, Israel).

The predefined dose escalation scheme, which was not segregated by study site, consisted of 2, 4 or 6 mg/kg WST11 activated by 200 or 300 J/cm light in a 3 + 3 dose escalation design to determine the MTD. The decision to escalate to the subsequent drug and/or light dose was determined by an independent DSMB after mpMRI obtained 1 week after treatment and assessment of treatment related AEs in each escalation stratile.

Stopping rules for dose escalation were defined in case of DLT, significant AEs (ie severe or serious drug related AEs), changes in safety laboratory parameters defined as grade 2 or greater according to NCI (National Cancer Institute) CTCAE (Common Terminology Criteria for AEs), unexpected or atypical MRI findings, or deterioration in electrocardiogram findings. DLT was defined as specific AEs graded as CTCAE grade 3 or greater