Androgen Deprivation Therapy Potentiates the Efficacy of Vascular Targeted Photodynamic Therapy of Prostate Cancer Xenografts

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Abstract

Purpose: WST11 vascular targeted photodynamic therapy (VTP) is a local ablation approach relying upon rapid, free-radical-mediated destruction of tumor vasculature. A phase III trial showed that VTP significantly reduced disease progression when compared with active surveillance in patients with low-risk prostate cancer. The aim of this study was to identify a druggable pathway that could be combined with VTP to improve its efficacy and applicability to higher risk prostate cancer tumors.

Experimental Design: Transcriptome analysis of VTP-treated tumors (LNCaP-AR xenografts) was used to identify a candidate pathway for combination therapy. The efficacy of the combination therapy was assessed in mice bearing LNCaP-AR or VCaP tumors.

Results: Gene set enrichment analysis identifies the enrichment of androgen-responsive gene sets within hours after VTP treatment, suggesting that the androgen receptor (AR) may be a viable target in combination with VTP. We tested this hypothesis in mice bearing LNCaP-AR xenograft tumors by using androgen deprivation therapy (ADT), degarelix, in combination with VTP. Compared with either ADT or VTP alone, a single dose of degarelix in concert with VTP significantly inhibited tumor growth. A sharp decline in serum prostate-specific antigen (PSA) confirmed AR inhibition in this group. Tumors treated by VTP and degarelix displayed intense terminal deoxynucleotidyl transferase–mediated dUTP nick-end labeling staining 7 days after treatment, supporting an increased apoptotic frequency underlying the effect on tumor inhibition.

Conclusions: Improvement of local tumor control following androgen deprivation combined with VTP provides the rationale and preliminary protocol parameters for clinical trials in patients presented with locally advanced prostate cancer.
Combination of ADT and VTP in Prostate Cancer Models

Translational Relevance
Targeting of the androgen receptor pathway is a key therapeutic strategy for prostate cancer. Androgen deprivation therapy (ADT) is the most effective treatment of metastases and is used as adjunctive therapy in combination with radiotherapy for whole gland ablation of intermediate/high-risk cancer. A recent multicenter phase III clinical trial in low-risk prostate cancer patients showed tumor ablation, minimal toxicity, and decreased localized progression by WST11 vascular targeted photodynamic therapy (VTP) compared with active surveillance. Transcriptome profiling provided herein shows an upregulated androgen response pathway following VTP. We hypothesized that targeting this pathway with short-course ADT in combination with VTP should significantly delay tumor growth compared with VTP or ADT monotherapies. Furthermore, because ADT and VTP have already been approved for treatment of prostate cancer, the proposed combination might translate rapidly into the clinic and expand the utility of VTP to populations with higher-risk, localized prostate cancer.

free of clinically significant cancer in the treated lobes and 76% of the treated patients had avoided a need for subsequent radical therapy (11). The efficacy of VTP could potentially be improved with a complementary, targeted combination therapy. Furthermore, combination therapy may allow for the extension of VTP treatment to additional cohorts of patients with high-risk localized prostate cancer.

The initial aim of this study was therefore to identify potential druggable pathways active in prostate cancer tumors exposed to VTP using transcriptome analysis. We identified a compensatory, acute upregulation of AR pathway activation following VTP treatment. As ADT to inhibit prosurvival signaling via androgen receptor (AR) is the mainstay treatment for aggressive prostate cancer, we then went on to confirm that inhibition of AR activity enhanced the efficacy of VTP treatment in prostate cancer xenograft models.

Materials and Methods

General
Lyophilized WST11 was obtained from Steba Biotech. Human prostate cancer cell lines VCaP was purchased from the ATCC, and LNCaP-AR was kindly provided by Dr. Charles Sawyers (MSKCC). Both cell lines were tested negative for mycoplasma using the MycoAlert PLUS Assay from Lonza and authenticated using Short Tandem Repeat analysis by ATCC. LNCaP-AR cells were cultured in RPMI supplemented with 10% FBS, 2 mmol/L glutamine, whereas VCaP cells were cultured in DMEM with high glucose, 10% FBS, and 2 mmol/L glutamine. All the components for cell culture were from Life Technologies. Degarelix was purchased from Ferring Pharmaceuticals Inc.

Animal models
All animal work was performed in accordance with a protocol approved by the Institutional Animal Care and Use Committee of Memorial Sloan Kettering Cancer Center. Subcutaneous tumors were established in intact male mice through injection of LNCaP-AR or VCaP human prostate cancer cell lines. We subcutaneously injected 2 × 10^6 LNCaP-AR cells in 100 µL of 1:1 media/Matrigel (BD Biosciences) into the hindlimb area of 6- to 8-week-old, male, athymic nude mice (NCl, Fredrick, MD) or severe combined immunodeficiency (SCID) mice (C.B-17<sup>scid</sup>/JtcTac–Prkdc<sup>scid</sup> Taconic). We also injected 2 × 10^6 VCaP cells into SCID mice (Taconic). Tumor growth was monitored by caliper measurement weekly. When the volume of tumors reached approximately 100 mm³, the animals were randomly assigned to different cohorts for further experiments.

 Treatments
VTP. An anesthetic cocktail of 150 mg/kg ketamine and 10 mg/kg xylazine was administered intraperitoneally prior to treatment and was supplemented with inhaled isoflurane. A single dose of carprofen (5 mg/kg) and 1 mL of subcutaneous warm saline were administered. WST11 was reconstituted in sterile 5% dextran in water at 2 mg/mL under light-protected condition, and the aliquots were stored at ~20°C. On the day of VTP treatment, an aliquot was thawed and filtered through 0.2 µm disc syringe filter (Sartorius Stedin Biotech North America). The mice were intravenously infused with WST11 via tail vein (9 mg/kg) followed immediately by 10-minute laser (Ceramoptec) illumination (755 nm, 100 mW/cm for transcriptome analyses, and 150 mW/cm for in vivo studies) through a 1-mm frontal fiber (MedLight S.A.). The light field was arranged to cover the entire tumor area plus 1 mm rim using red-light aiming beam.

ADT. Single dose of degarelix was administered at 0.5 mg per mouse at 3 days before VTP treatment via subcutaneous or intraperitoneal injection. Drug administration was initiated when tumor size reached approximately 100 mm³.

PSA detection in serum
Free PSA and total PSA were measured with a dual-label immunofluorometric assay (DELFIA Prostatus PSA Free/Total PSA; Perkin-Elmer Life Sciences) according to the manufacturer's recommendations. This assay measures free PSA and complexed PSA in an equimolar fashion (12, 13), and the cross-reactivity of PSA;ACT for free PSA is less than 0.2% (14). The lower limits of detection are 0.1 ng/mL for both total PSA and free PSA. For detection, the 1235 automatic immunoassay system from Perkin-Elmer Life Sciences was used.

Histology and immunohistochemistry
All tumor specimens were fixed in 10% buffered formalin (Fisher Scientific), processed routinely, embedded in paraffin, sectioned at 5-µm thickness, and stained with hematoxylin–eosin (H&E). Immunohistochemistry (IHC) of tumors was performed on 5-µm formalin-fixed paraffin embedded (FFPE) section following heat-induced epitope retrieval (HIER) in a buffer at pH 9.0. AR staining with anti-AR antibody (at 0.66 µg/mL; Abcam) and terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) staining for cell death were performed. A single dose of degarelix was administered at 0.5 mg per mouse at 3 days before VTP treatment via subcutaneous or intraperitoneal injection. Drug administration was initiated when tumor size reached approximately 100 mm³.

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was applied at a concentration of 1:250 and 1:100, respectively, followed by application of a polymer detection system (DS9800, Novocastra Bond Polymer Refine Detection; Leica Biosystems). For all IHC stains and TUNEL, the chromogen was 3,3 diaminobenzidine tetrachloride (DAB), and sections were counterstained with hematoxylin. For quantification of CD31, Ki67, and TUNEL staining, whole slide digital images were generated on a scanner (Pannoramic 250 Flash III, 3DHistech, 20x/0.8NA objective) at a resolution of 0.2431 μm per pixel. Staining quantification was performed with QuPath 0.1.2 software (Centre for Cancer Research & Cell Biology, Queen’s University Belfast, UK). For CD31 and Ki67, the region of interest (ROI) was defined as viable tumor tissue excluding necrosis. For TUNEL, the ROI was defined as total tumor tissue including necrosis. For CD31 and TUNEL, the positive area, defined as the ratio of DAB-stained pixels to total ROI area, was measured using the positive pixel count algorithm. For Ki67, the ratio (percentage) of cells with positive nuclear staining to total cell number was measured with the positive cell detection algorithm. ROI selection, algorithm optimization and validation, and qualitative examination of H&E slides were performed by a board-certified veterinary pathologist (S. Monette).

Gene set enrichment analysis for transcriptome analysis of LNCaP-AR xenografts following VTP treatment

LNCaP-AR xenografts were established in intact SCID mice by injecting 2 million cells as described previously (16) and, once established, were treated with VTP at 9 mg/kg WST11 followed by 100 mW laser fluence. Tumors were collected at 3, 6, or 24 hours, 1 week, and 8.5 weeks post VTP, and RNA was isolated following the standard protocol using TRIzol (Fisher Scientific). Expression profiling was performed using Illumina HT-12 Expression BeadChip array, and the data were analyzed using Partek Genomics Suite (Partek Inc.). The microarray data then underwent secondary analysis by gene set enrichment analysis (GSEA; ref. 17) using gene sets from the Hallmark and C2, Canonical Pathways collections (Molecular Signature Databases v6.0 (MSigDB); Broad Institute: http://software.broadinstitute.org/gsea/msigdb). GSEA| MSigDB. Accessed 19 Jun 2017. Microarray data have been

Figure 1.
Transcriptome analysis of LNCaP-AR human prostate cancer xenografts after VTP treatment. A, Top-ranked GSEA pathways among the gene sets HALLMARK and Canonical Pathways (C2). B, Enrichment plots with normalized enrichment scores (NES) for androgen response pathways within both gene sets at 6 hours post-VTP (n = 4) vs. control (n = 4).
deposited in the National Center for Biotechnology Information Gene Expression Omnibus (GSE109681).

Statistical analysis

Two-way ANOVA test using GraphPad Prism (GraphPad Software) was used for therapeutic efficacy in affecting tumor growth, one-way ANOVA for PSA, and a Mann–Whitney test for CD31, Ki67, or TUNEL staining quantification. Differences with 

Results

Transcriptome analysis of VTP-treated tumors by GSEA revealed an enrichment of androgen response pathways

To identify potential druggable pathways active in prostate cancer that could be exploited for combination therapy with VTP, we analyzed the transcriptome of LNCaP-AR xenograft tumors following acute VTP exposure. Unbiased GSEA identified statistically significant enrichments with gene sets related to hypoxia, HIF1A, and VEGFR pathways at 3 to 6 hours after VTP treatment (Fig. 1, Supplementary Tables S1 and S2), effects that have previously been shown to be associated with photodynamic therapies (PDT; ref. 18). Interestingly, AR signaling gene sets were also upregulated in VTP-treated tumors compared with control mice, suggesting that the AR may be a viable target for combination therapy with VTP.

Combination therapy of ADT with VTP suppressed tumor growth to a greater extent than either treatment alone

To test our hypothesis that the preemptive blocking of androgen signaling upregulation induced by VTP might improve the outcome of tumor growth control, we tested the combination of VTP with an androgen signaling pathway inhibitor in widespread clinical use for the treatment of prostate cancer. Degarelix is a long-acting, gonadotropin-releasing hormone antagonist that results in a rapid onset of medical castration (19, 20). To establish preexisting AR inhibition, treatment with degarelix was initiated 3 days prior to administering VTP to prostate cancer xenograft tumors. Prior studies with VTP established that components of the immune response contributed to the anticancer activity of VTP (21). We therefore compared the efficacy of the combination therapy against LNCaP-AR tumors in both athymic nude (T-cell deficient; Fig. 2A) and SCID (both T- and B-cell deficient; Fig. 2B) mice. Tumor-bearing nude mice were randomly assigned to four cohorts: control (n = 7), degarelix (n = 9), VTP (n = 8), and degarelix + VTP (n = 9), and tumor size was measured weekly. The combination treatment suppressed tumor growth more efficiently (P < 0.01 for combination vs. degarelix, P < 0.005 for combination vs. VTP). B, Combination of degarelix and VTP on tumor growth in SCID mice. Mice bearing LNCaP-AR tumors were randomly assigned to 4 cohorts: control (n = 14), degarelix (n = 14), VTP (n = 17), and degarelix + VTP (n = 16), and tumor size was measured weekly (P < 0.0001, combination vs. degarelix or VTP). Results were combined from two separate experiments. One dose of degarelix was given at 3 days prior to VTP.

Figure 2.

Efficacy of the ADT and VTP combination in the LNCaP-AR human prostate cancer model. A, Degarelix and VTP combination on tumor growth in athymic nude mice. Mice bearing LNCaP-AR tumors were randomly assigned to 4 cohorts: control (n = 7), degarelix (n = 9), VTP (n = 8), and degarelix + VTP (n = 9), and tumor size was measured weekly. The combination treatment suppressed tumor growth more efficiently (P < 0.01 for combination vs. degarelix, P < 0.005 for combination vs. VTP). B, Combination of degarelix and VTP on tumor growth in SCID mice. Mice bearing LNCaP-AR tumors were randomly assigned to 4 cohorts: control (n = 14), degarelix (n = 14), VTP (n = 17), and degarelix + VTP (n = 16), and tumor size was measured weekly (P < 0.0001, combination vs. degarelix or VTP). Results were combined from two separate experiments. One dose of degarelix was given at 3 days prior to VTP.
cohorts: control, degarelix, VTP, and degarelix and VTP combination. The combination of degarelix and VTP resulted in statistically significant improved tumor growth control compared with either degarelix ($P < 0.01$) or VTP alone ($P < 0.005$; Fig. 2A). As in the nude mouse, the combination of degarelix and VTP led to superior control of LNCaP-AR tumor growth in SCID mice ($P < 0.0001$ for either monotherapy vs. combination; Fig. 2B). The combination of degarelix and VTP was also significantly more effective than VTP alone ($P < 0.005$; Fig. 3) in delaying the growth of VCaP, a human prostate cancer model with AR gene amplification that also expresses the constitutively active AR splice variant, AR-V7.

Combination therapy of ADT and VTP was more effective than VTP alone in downregulation of total PSA levels and induction of apoptosis/necrosis

To verify that AR activity was inhibited by the treatments, we measured the levels of total PSA (tPSA) in serum of mice bearing LNCaP-AR tumors (Fig. 4A). tPSA values were determined in separate cohorts of mice at 1, 3, or 7 days post-VTP (4, 6, or 10 days post degarelix). tPSA values declined by either VTP or degarelix alone, but the sharpest drop in tPSA levels was seen with the combination of degarelix and VTP ($P < 0.05$ vs. control across all time points).

In parallel, we assessed the histology of degarelix and/or VTP-treated tumors on days 3 and 7 post-VTP by both H&E and TUNEL assay to detect cell death (apoptotic and/or necrotic cells; Fig. 4B). VTP-treated tumors displayed partial cell death characterized by large foci of TUNEL staining, but with significant TUNEL-negative areas. Tumors treated with combination therapy appeared to display more extensive areas of TUNEL staining. Although not statistically significant compared with VTP alone, there were fewer tumors that escaped cell death in the combination group, suggesting that increased cell death underlies the effect on tumor inhibition. In contrast, degarelix alone–treated tumors exhibited little TUNEL staining, but still showed reduced Ki67 signal compared with controls, as expected ($P < 0.05$, Supplementary Fig. S1). These findings are reminiscent of patient studies, which have reported overall low frequencies of apoptosis in prostate cancer following ADT (22, 23). Nuclear AR staining was inversely correlated with TUNEL, suggesting that viable AR-positive cells had escaped focal therapy effects of VTP alone. Notably, the tumors treated with combination therapy were absent of AR staining, suggesting that remaining viable tumor cells were few in number.

ADT reduces tumor vessel staining

CD31 is primarily a marker for endothelial cells which can help evaluate the degree of intratumoral vessel formation. The degarelix-treated tumors appear to have less vessels than tumors in the control group as shown in Fig. 5A. The quantification of staining area depicts a 38% decrease in CD31 in degarelix-treated tumors compared with tumors ($P < 0.05$) in the control group. This might be a contributing factor of reduction in tumor recurrence in ADT/VTP combination group, although we did not observe any...
significant difference in CD31 vessel counts between the combination and VTP groups with the caveat that there was minimal remaining viable tumor material in these two groups (Supplementary Fig. S2).

Discussion

The effective adoption of prostate cancer screening has led to earlier detection of small, clinically significant prostate cancers amenable to the newly developed treatment strategies for partial gland ablation which are well tolerated and associated with fewer adverse side effects than aggressive radical therapies such as surgery and radiotherapy. Positive oncologic outcomes in clinical studies of VTP have led to the recent approval of TOOKAD Soluble for the treatment of low-risk prostate cancer and highlight the potential of VTP to serve as an alternative to active surveillance or radical therapies (9–11). To potentially extend VTP treatment to larger cohorts of patients, we have recently launched a VTP clinical
trial (NCT03315754) for patients with localized prostate cancer of intermediate risk, Grade Group 2 [Gleason score 7 (3+4)]. However, adaptation of this treatment to slightly larger and more aggressive tumors has potential risk for undertreatment, prompting the need for augmenting the mechanism of VTP-mediated tissue necrosis.

A byproduct of the oxidative damage triggered by PDT is the induction of intrinsic cellular stress response pathways, and these are thought to contribute to cancer cell survival and therapy resistance (18). To identify stress response pathways amenable to pharmaceutical intervention that could be used in conjunction with VTP, we performed transcriptome and GSEA of VTP-treated human prostate xenograft tumors. Consistent with earlier studies of PDT in cancer (18), we observed the upregulation of gene sets related to hypoxia/HIF1α, VEGFR, AP-1, and NF-kB in the immediate hours following VTP exposure. In addition, other potential cell survival pathways such as EGF/EGFR were also enriched after VTP. Although EGFR inhibitors (erlotinib, gefitinib, and lapatinib) have been clinically evaluated for prostate cancer, these phase II trials were limited to those with advanced or metastatic disease and displayed clinical benefit in only a small subset of patients [lapatinib (24, 25), erlotinib (26, 27), and gefitinib (28)]. However, of particular interest to our study was the finding that VTP treatment resulted in the acute upregulation of pathways related to AR signaling. Targeted AR inhibition forms the cornerstone of therapy for metastatic prostate cancer (29) and is the standard of care in the neoadjuvant or adjuvant setting for high-risk localized disease treated with external-beam radiotherapy (EBRT; ref. 30). AR inhibition is also being increasingly explored in clinical trials as neoadjuvant or adjuvant treatment for surgical patients with intermediate- to high-risk localized prostate cancer. Thus, there is supporting rationale for targeting AR in the setting of VTP-mediated tissue ablation for prostate cancer.

ADT can be accomplished by orchietomy, but is more commonly achieved medically through the use of gonadotropin-releasing hormone (GnRH) agonists (leuprolide, goserelin, triptorelin) or more recently, antagonists (degarelix). GnRH agonists are known to cause an initial surge in circulating testosterone levels before achieving castration levels. In contrast, degarelix results in rapid castration in both men and mice without the testosterone flare (31, 32). In nude mice, a GnRH antagonist modestly outperformed an agonist in growth inhibition of a prostate cancer xenograft (33).

We chose degarelix to test the hypothesis that neoadjuvant ADT may improve antitumor efficacy of VTP in mice bearing prostate cancer xenograft tumors. In multiple model systems, the combination of degarelix and VTP offered superior local tumor growth inhibition compared with either degarelix or VTP alone. The combination-treated group displayed fewer tumors that escaped cell death compared with VTP alone. We did not detect a substantial induction of apoptosis in the tumors treated with degarelix alone, which is consistent with clinical reports demonstrating that prostate cancer apoptosis is not commonly seen in patients after ADT (22, 23). Treatment success was also demonstrated by AR inhibition that was reflected in the significant reduction in serum PSA levels, which was most extensive in the combination group.

Induction of tumor hypoxia following PDT with subsequent activation of cellular survival pathways and angiogenesis are potential factors that could adversely affect VTP treatment response (18). In prostate cancer cells, androgens promote the expression of HIF1α and VEGF (34, 35), and HIF1α enhances the activity of AR signaling (36, 37). Thus, the hypoxic tumor microenvironment induced by VTP with corresponding HIF1α upregulation could result in promotion of protumorigenic AR signaling, which is consistent with the results of our gene set analysis. Studies in prostate cancer patients have demonstrated that tumor hypoxia and HIF1α are decreased following ADT (38, 39). In prostate cancer model systems, ADT decreases VEGF production and reduces tumor vascularization (40–42) corresponding to the decrease in CD31-positive staining of endothelial cells following degarelix treatment in this study. Thus, we propose that ADT potentiates the efficacy of VTP treatment at least in part by counterbalancing the protumorigenic effects of hypoxia and angiogenesis.

Our findings draw parallels with the use of neoadjuvant and adjuvant ADT in combination with EBRT, which was first demonstrated 20 years ago to extend survival in patients with locally advanced prostate cancer (43, 44). If the combination of ADT and VTP is found effective in the clinical setting, this strategy may provide means for effective treatment of locally advanced prostate cancer with significantly less side effects than the current approaches.

Disclosure of Potential Conflicts of Interest
K. Kim, P.A. Watson, A. Scherz, and J.A. Coleman are listed as co-inventors on a provisional patent application on VTP and combination therapy that is owned by Memorial Sloan Kettering Cancer Center and the Weizmann Institute of Science. H. Lilja holds ownership interest (including patents) in free PSA, hK2, and intact PSA assays, and is named on a patent for a statistical method to detect prostate cancer licensed by OPKO Health. No potential conflicts of interest were disclosed by the other authors.

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