Medium-term follow-up of Vascular-Targeted Photodynamic therapy (VTP) of localized prostate cancer using TOOKAD®-Soluble WST-11 (Phase II trials)

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Abstract

Background and Objective:

To assess the medium term tumor control in patients with localized prostate cancer treated with vascular-targeted photodynamic therapy with TOOKAD®-Soluble WST11 (VTP). To assess the medium term tolerability of the treatment.

Design, Setting, Participants, and Intervention:

During the clinical phase II studies, 68 patients were treated with VTP under optimal treatment conditions (WST11 at 4mg/kg, light energy at 200J/cm and a light density index ≥1) and have been included in a 3.5-year follow-up.

Outcome Measurements and Statistical Analysis:

Post-interventional visits were scheduled every 6 months and conducted as per local standard practice in each study center. Cancer free status was assessed by means of PSA kinetics, multiparametric MRI and/or prostate biopsies.

Results and Limitation:

At the end of the 3.5 years follow-up, overall successful focal ablation was achieved for 51 patients (75%). Cancer was identified in the untreated lobe in 17 patients (25%). In total, 34 patients (50%) were cancer free in both prostate lobes. In case of recurrent/persistent malignancy, the Gleason score remained consistent or changed at the maximum by 1 point (upgrading by 1 Gleason point to 3+4 for 8 patients and 4+3 for 2 patients). There were 64 related adverse events: 48% were Clavien grade I, 47% were grade II and 5% were grade III. There were no Clavien grade IV and V

adverse events. Limitations are small sample size and heterogeneity in the follow-up for some centers.

Conclusions

VTP was a safe and efficient treatment and represents an alternative option for localized **low risk** prostate cancer management over the medium term. Precise diagnostic methods and imaging tools are thereby essential requirements to ensure safe and complete targeted therapy.

Patient summary

In this report we looked at the medium term outcomes of focal photodynamic therapy for early-stage prostate cancer. We found that this form of treatment is efficient and **might have the potential to become a therapeutic option for low-risk cancer** ~~represents an alternative to surveillance, surgery or radiation~~. Effectiveness depends on precise diagnostic methods as MRI and accurate biopsy.

Introduction

Prostate cancer (PCa) is diagnosed earlier nowadays, often at a localized stage and at a lower overall risk to the patient[1]. In low to moderate risk disease, the therapeutic index when whole-gland treatment is applied, in the form of radiation therapy or surgery, is low[2,3]. Tissue-preserving treatment strategies such as that conferred by vascular-targeted photodynamic therapy (VTP) aim to reduce the side-effect profile significantly, to maintain quality of life and to achieve similar oncological efficacy, in other words: maintaining the benefits and reducing the harms[4].

Basically, VTP induces focal ablation of tumor lesions, through cell necrosis by damaging the tumor vasculature. VTP destroys targeted tissues using a photosensitizer (TOOKAD® Soluble (WST11), STEBA Biotech) in association with a low power near-infrared laser in the presence of oxygen. WST-11 absorbs light and transfers energy to oxygen molecules creating reactive oxygen species inducing local vascular occlusion and cell destruction[5].

Among various approaches to focal therapy of prostate carcinoma, VTP is the only one that has recently been evaluated in a multi-center, randomized, controlled phase III trial[6]. This study could demonstrate a significantly **superior oncologic outcome** by hemigland VTP compared to active surveillance within in the two years follow-up. Likewise, most other studies evaluating focal therapy have been short term. This report aims to provide medium term data in a prospectively evaluated cohort of men included in two registered studies (NCT00975429 PCM201 and NCT00707356 PCM203). It builds on previously published work that has addressed safety, dosimetry and early results[7–9]. The close correlation between dose and tissue necrosis volume allowed defining optimal treatment parameters including drug dose, energy delivery and targeting[10].

Patients and Methods

We report on the medium-term follow-up of two prospective, multicenter, open-label, multiple-arm, dose-escalation, non-randomized phase II studies with TOOKAD®-Soluble VTP (NCT00707356 and NCT00975429). The study was conducted according to ICH standards and was done with full ethics committee approval granted for each center. Eight centers in Europe and one in Canada recruited patients from 2008 to 2010. An approved protocol amendment and new contracts with participating centers permitted us to prolong the follow-up period. Follow-up was implemented as per local standard of care between 2009 and 2014.

The phase II study results have been published and provided a description of the optimal treatment conditions[8,9]. 125 men with localized PCa eligible for active surveillance were included (Gleason 3+3 maximum; PSA < 10 ng/ml; clinical stage up to T2a). Within protocol men were treated by hemi-ablation with a combination of drug dose, light dose (4 or 6 mg/kg WST11 and 200 or 300 J/cm) and fiber lengths and number. The fiber component was contingent on the volume of tissue that defined the target. This was a function of prostate volume. Treatment planning under optimal conditions was predicated on a 4 mg/kg dosing and a light energy of 200 J/cm of fibers in order to generate a light density index (LDI) ≥1[11]. All patients were followed-up according to planned study visits. Within the protocol of both phase 2 studies there existed the opportunity to re-treat patients **by VTP** who were identified as having prostate cancer on the systematically performed six-month biopsy. **However, patients were free to choose whole gland treatment which was not**

further specified by study protocol and was basically conducted as per local standard of care or patients´ choice (prostatectomy, brachytherapy, HiFU). In cases of re-treatment a 6-month period of follow-up within protocol was required.

This report uses data that was collected after the last study visit. The collected data were derived from each center in a prospective manner but reflected the standard care to which men were returned to after study completion. Therefore, this is a report of definable events that occurred during the period of post-study surveillance that lasted 3.5 years (seven evaluation periods every six months). The endpoint of the clinical phase II studies at month six thus correlates with the first evaluation period of the presented follow-up. Key data points comprised PSA, reports from imaging such as mp-MRI, results from any prostate biopsies and the occurrence of any intervention. Any adverse events that were documented during this period of surveillance were handled according to the Clavien classification.

The data analyses of quantitative variables were calculated using descriptive statistics (n; mean; standard deviation; median; minimum; maximum). Qualitative variables were assessed by means of frequency count by category. Individual listings were added.

Results

In total, 68/125 patients were treated under optimal conditions (4 mg/kg of TOOKAD®-Soluble, 200 J/cm of laser light energy and a LDI≥1) in the 2 phase II studies (table 1). **The remaining 57 patients treated within these dose escalation studies had not received optimum treatment conditions (based on control MRI and biopsy). Radiographic and histopathological outcomes are reported elsewhere**[8,9,11]**, however, data were not used for mid-term follow-up. Two of the 68 optimally treated patients** ~~Two of the patients~~ were not evaluable during the follow-up period and have been excluded. A further 14 patients underwent interventional treatment for prostate cancer (8 radical surgery, 5 brachytherapy and 1 high intensity focused ultrasound, HIFU) and could therefore not be monitored for treatment effect or WST-11 related toxicity (figure 1). These patients had at least 1 positive biopsy during the follow-up and decided to have immediate whole-gland treatment. In 8/14 patients, positive cores were from the VTP treated lobe. Gleason score was unchanged at 6(3+3) in 7 patients (5 radical surgery, 1 brachytherapy, 1 HIFU); Gleason score was at 7(3+4) in 5 patients (3 brachytherapy, 2 radical surgery) and was at 7(4+3) in 2 patients (1 radical surgery, 1 brachytherapy). Eleven patients (6 radical surgery, 4 brachytherapy, 1 HIFU) had a MRI before the intervention, which showed suspicious lesions in 10 cases (one MRI-result was unclear because of adjacent scar tissue). Histopathological characteristics of the surgical specimen after VTP and radical prostatectomy have been recently published[12].

Fifty-two patients were amenable to surveillance for the 3.5-year follow-up (table 1). During this time the patients underwent a mean (median) of 4.8 (5) follow-up visits. In the first 18 months after the VTP over 90% of patients were assessed. In the

subsequent 24 months fewer men underwent examination due to a decreased need with time.

Mean (SD) age at first VTP was 62,6 years (5,6). All patients had a baseline Gleason score of 6 and at least one positive core. The mean (SD) number of positive cores was 2,0 (1,0) with a mean (SD) total cancer core length of 4,2 mm (3,8). In 10 cases positive biopsies were found bilaterally, however, 13 (19%) patients received bilateral treatment (3 patients with initial unilateral treatment and a further treatment of the contralateral side after a positive biopsy at month 6 on the other side). All other patients were treated unilaterally. Mean (SD) LDI was 1,45 (0,35).

At the end of the 3.5 years of standard care follow-up, successful focal ablation was documented for 75%, i.e. 51 patients remained cancer free in the treated lobe. Cancer was identified in the untreated lobe in 17/68 patients (25%). In total, 34/68 patients (50%) were cancer free in both prostate lobes.

A total of 100 prostate biopsies were performed during the 3.5-year follow-up (table 1). Most of these (n=67) took place during the early phase of follow-up. Overall, 40 biopsies showed malignancy. The mean (median) number of positive cores per biopsy was 2.3 (2) and the mean (median) cancer core length was 5.79 mm (4mm). Analyzing the change in Gleason score from the initial screening biopsies, 8 patients with cancer persistence had an upgrading by 1 Gleason point (6 patients: 3+4; 2 patients: 4+3). No greater upgrading was documented.

Six months after VTP, the mean (median) PSA level was reduced by -2.64 ng/ml (-2.80 ng/ml) from the pretreatment baseline level of 5.97 ng/ml (5.70 ng/ml). Mean

results were stable (figure 2). However, PSA level changes should be assessed with particular caution because of the high number (81%) of unilateral treatment.

MR imaging was performed on an irregular basis during follow-up. All in all, 32 MRI scans were conducted and 20 scans were **suspicious for** ~~able to detect or confirm~~ persistent malignancy. **Of these 20 MRIs, 6 showed suspect lesions in the untreated lobe and 14 showed pathological enhancement of the treated lobe. In the majority of cases (18/20), malignancy was confirmed by transrectal biopsy during follow-up.**

In terms of safety and tolerability of VTP, 84 adverse events (AEs) were reported in total, among which, 20 AEs were not related to the study drug, device or procedure and rather due to other medical conditions. Of the 64 related AEs (table 2), 48% were Clavien I, 47% were Clavien II and 5% were Clavien III. There were no Clavien IV or V. The most frequently assessed AEs were erectile dysfunction (n=28), lower urinary tract symptoms (n=14) and perineal pain (n=9). In the course of follow-up, the number of AEs documented was the highest at 6 months with 40.5 % (34/84 AEs) and eventually decreased afterwards (12 months: 23.8%; 18 months: 11.9%; 24 months: 15.5%; 30 months: 5.9%; 36 months: 1.2%; 42 months: 1.2%). Erectile dysfunction was reported by 11 (16.2 %) patients at 6 months and by 9 (15.8%) patients at 12 months, while only 3 patients (5.4%) were affected 18 months after VTP (24 months: 3 patients; 30 months: 1 patient; 36 months: 0; 42 months: 1 patient). **In total, 18/68 patients (26.5 %) experienced erectile dysfunction at any time during follow-up.** No specific treatment for ED was reported.

The three severe AEs were reported at 6 and 12 months and were related to the study procedure and/or treatment device. At 6 months, one patient reported hematuria, another received treatment due to an orchitis. At 12 months, one patient had prostatitis and was hospitalized after diagnosis. All three patients were treated according to standard of care and recovered without sequelae.

Discussion

Recently, the results of a randomized controlled trial phase III trial of over 400 men conducted in 47 European university centers and community hospitals and comparing hemigland VTP to standard of care, active surveillance, were published[6]. This study represents the only phase III study in the field of focal therapy. Over the 24 months follow-up, it demonstrated a ~~significantly~~ **superior oncologic outcome** (49% vs. 14% negative rebiopsy results, 28% vs. 58% progression to high/intermediate risk). We now set out to evaluate mid-term outcome of VTP by evaluating a cohort of men included in two registered phase II studies (NCT00975429 PCM201 and NCT00707356 PCM203) over a 3.5 years follow-up.

In summary, the surveillance of patients treated with WST-11 VTP in the early phase studies has demonstrated good tolerability. Three quarters (75%) of the eligible patients **(51/68 patients)** were free of disease within the treated lobe 3.5 years after completing the study protocol. **17 patients had cancer in the contralateral lobe, leaving 34/68 patients (50%) cancer free in both lobes.** Of those patients who were identified as having prostate cancer during the period of surveillance, half were of low-malignant potential (18/34 patients), characterized by exclusive Gleason 3 pattern and of low volume. 11% of patients had histopathological upgrading during

follow-up. **This number is favorable and slightly better than most active surveillance series - although worse than others: Eggener et al. reported the upgrade in their study to be as low as 5.7% [13]. This number certainly begs the question of the necessity of focal treatment in low-risk and very-low-risk patients, particularly with over 25% of patients experiencing erectile dysfuction in the present study. Due to the fact that active surveillance is associated with the least decision regret compared to other treatments**[14] **focal therapy seems rather unlikely to become a serious alternative option for patients suitable for active surveillance.**

This study suffers from several limitations: the small sample size and a certain extent of heterogeneity in the follow-up for some centers. However, these results need to be interpreted within the context of the pooled data. The ideal design would have been a long-term protocol with mandated follow-up, protocol-mandated biopsy and precise criteria for repeated prostate biopsies. This type of design is not normally favored for early phase studies that are designed to recruit quickly and realize their pre-defined endpoints in order to inform later phase studies. An appropriate alternative would have been to undertake formal data linkage studies so that events are recorded as they happen. The design is appealing and increasingly possible due to electronic patient records but was not feasible within different jurisdictions at the time when these studies were conducted. We therefore feel that whilst in no way perfect, the data derived in this study is useful for planning future studies and for advising patients. Another important point is the relevance of these data sets as they are the first over the medium term.

The opportunity to observe selectively treated prostate tissue over a 3.5-year period is fairly novel but not unique. Bahn et al reported their medium term follow-up of patients with focal cryotherapy outside of a study protocol[15]. Our results are remarkably similar given that in their series 75% of patients that underwent post-cryotherapy biopsy were free of prostate cancer. Both series have the issues that biopsies were not applied in all patients at given time points. Both report a reduction in the intensity of biopsies over time. The Bahn series however did not have the benefit of mp-MRI that increasingly appears to be replacing biopsy in the post ablation period[16].

One issue that all these studies share is the certainty that we can entertain on exactly where in the treated prostate we are sampling during the period of post-treatment surveillance. Sampling a small volume of scar tissue (typically a 20cc lobe will reduce to a 3-5cc remnant) which is hard to see (echo poor on grey scale ultrasound) and hard to biopsy (as scar tissue is not captured easily). Hopefully imaging will assist in the follow-up of these men and permit those that are free of disease to avoid biopsy, but at the same time provide a target for those that appear at risk of recurrence. There is almost certainly going to be a role for image registration systems to assist in the targeting of the treated area or the small focus of vascularity that is seen of the T1 weighted dynamic gadolinium scans[17]. This latter manifestation of perfusion in an area where there should be very little perfusion confers a high positive predictive value for recurrent disease in treated tissue[16]. **However, mpMRI does not allow the exclusion of Gleason 3+3 or 3+4 recurrent disease with certainty. As recently shown by both PROMIS**[18] **and PICTURE** [19] **study, mpMRI is almost incapable of detecting Gleason 3+3 or small volume 3+4 disease.**

Our results are very encouraging in many ways. First, they are from early phase studies that were principally addressing safety issues. Many of these treatments were conducted by clinicians and teams that were early in their adoption of the technology and therefore at the beginning of their learning curves. This is an inevitable phase of health care technology development. It is therefore likely that the quality of the treatments in terms of case selection, treatment performing and optimization of follow-up will all serve to improve the oncological efficacy going forward.

Secondly, risk stratification methods are changing rapidly in prostate cancer. The reported patients in this study were all diagnosed using systematic TRUS biopsies, which is associated with considerable error. Recent reports, constituting level one evidence, indicate that a diagnostic process based on mp-MRI and image guided biopsy is going to become the new standard[20,21]. Underdiagnosis and inaccurate biopsy sampling may cause serious risks of under- and overtreatment of PCa[22,23]. This transition should result in more accurate risk stratification, which again should serve to improve the treatment procedure and decrease the positive biopsies that occur out of field[17].

Third, our results help but do not resolve the critical biological issue in relation to focal therapy. Are prostate cancers clonal in origin or are they transitional[24]? In other words, do they arrive at their biological potential early in their development or do aggressive cancers arise from less aggressive cancers over time? In this case, when do selective pressures occur? The relative stability of the treated lobe, once

rendered disease free might suggest the former. The absence of progression to high-risk cancers either within or outside the field of treatment might do the same. Recent data exploring the molecular differences between low and high-risk lesions support the clonal view[25,26]. Clearly, much more data is needed but a selective approach to prostate cancer- which is the way, in which all other solid cancers are managed- will work better if the clonal hypothesis dominates the developmental biology of these tumors.

Conclusions

VTP was a safe and efficient treatment and represents an alternative focal treatment option for localized prostate cancer management over the medium term. Precise diagnostic methods and imaging tools are thereby essential requirements to ensure safe and complete targeted therapy.

Patient summary

In this report we looked at the medium term outcomes of focal photodynamic therapy for early-stage prostate cancer. We found that this form of treatment is efficient and **might have the potential to become a therapeutic option for low-risk cancer** ~~represents an alternative to surveillance, surgery or radiation~~. Effectiveness depends on precise diagnostic methods as MRI and accurate biopsy.

Conflict of interests – disclosure

RA and ME are lecturers and proctors for the VTP procedure. FB and BG are/were employees of Steba. EB, CG and CGS received payment from Steba. AN received a travel grant from STEBA to collect data.

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Figure Legends

Figure 1: Treatment diagram

Figure 2: PSA levels

Table 1: Population characteristics and follow-up

Table 2: Adverse events