Photodynamic Therapy of Bladder Cancer – A Phase I Study Using Hexaminolevulinate (HAL)

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Abstract

Objectives: To assess the safety and feasibility of hexaminolevulinate (HAL) based photodynamic therapy (PDT) as adjuvant treatment after transurethral resection of the bladder (TURB) in patients with intermediate or high-risk urothelial cell carcinoma (UCC) of the bladder.

Materials and methods: Seventeen patients received 50 ml of either a 16 mM (4 patients) or 8 mM HAL (13 patients) solution instilled intravesically. Bladder wall irradiation was performed using an incoherent white light source coupled via a quartz fiber assembled into a flexible transurethral irrigation catheter. Each patient received 3 treatments with HAL-PDT 6 weeks apart. After PDT, patients were followed by regular cystoscopy for up to 21 months to assess time to recurrence. Reported adverse events (AEs) were coded according the World Health Organization Adverse Reaction Terminology (WHO-ART). Efficacy was assessed by cystoscopy, cytology, and histology, and was defined as the number of patients who were tumor-free at 6 or 21 months after initial PDT treatment. Transient bladder irritability was reported by 15 of the 17 patients and resolved completely in all patients. No evidence of a cumulative effect of treatment on the incidence of AEs could be detected. PDT treatment was performed without any technical complications. Furthermore preliminary assessment of efficacy showed that of the 17 patients included, 9 (52.9%; 95% CI: 27.8 –77.0) were tumor-free at 6 months, 4 (23.5%; 95% CI: 6.8 – 49.9) were tumor-free at 9 months, and 2 (11.8%, 95% CI: 1.5–36.4) were tumor-free after 21 months.

Conclusions: PDT using hexaminolevulinate and an incoherent white light system with the special flexible irradiation catheter system is technically feasible and safe and may offer an alternative in the treatment of non-muscle-invasive intermediate and high-risk bladder cancer. © 2013 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Photodynamic therapy; Hexaminolevulinate; Protoporphyrin fluorescence

1. Introduction

Non-muscle-invasive bladder cancer is currently treated by transurethral resection (TURB) and/or fulguration. However, recurrence and progression rates following endoscopic treatment of visible lesions are significant. The probabilities of recurrence range from about 15% to 61% at 1 year and from 31% to 78% at 5 years; the progression rate ranges from about 1% to 17% at 1 year and from 1% to 45% at 5 years [1]. To prevent recurrent and progressive disease, adjuvant intravesical chemotherapy and immunotherapy are applied. There is also rising interest in new therapeutic strategies such as photodynamic therapy (PDT). PDT has been shown to be effective in even bacillus Calmette-Guerin (BCG) refractory UCC and might offer a potential alternative for patients indicated for cystectomy [2].

The PDT mechanism relies on a specific light interaction with a photosensitised target tissue. The first generation

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photosensitizers (hematoporphyrin derivatives) used for treatment of bladder cancer showed severe side effects, including bladder shrinkage and long-term cutaneous photosensitization [3]. Photosensitizers of the second generation based on endogenous photoactive porphyrins like protoporphyrin IX (PpIX), which are synthesized intracellularly upon topical administration of 5-aminolevulinic acid (5-ALA) or its derivatives, overcome these side effects [4]. Several studies of PDT with 5-ALA demonstrated promising clinical results [2,5–8]. Esterification of 5-ALA into more lipophilic derivatives such as hexaminolevulinate (HAL) results in 2-fold increase of PpIX fluorescence intensity and a more homogeneous drug distribution throughout all urothelial layers using 20-fold lower concentrations compared to the parent compound 5-ALA [9]. Due to the low PPIX-levels found in connective and muscle tissue, side effects attributable to an over dosage of light are thus practically excluded [10–12]. HAL has been approved for photodynamic detection (PDD) of bladder cancer in Europe and the United States [13–18]. We report on the first prospective clinical trial using HAL and a white light system for PDT of UCC of the bladder. The objective of this phase I study was to assess the safety and feasibility of PDT in patients with intermediate or high-risk bladder cancer.

2. Material and methods

2.1. Patients

Two centers enrolled 17 patients with histologically confirmed intermediate or high-risk non-muscle-invasive UCC of the bladder. Inclusion criteria were either low-grade early recurrence within 6 months after local chemotherapy or BCG, recurrent TaG3 and/or CIS, or recurrent T1 if not eligible for cystectomy as judged by the investigator or due to patient refusal.

Exclusion criteria were defined as muscle invasive disease (≥T2), history of upper tract urothelial cell carcinoma, a bladder capacity <200 ml, patients with porphyria, gross hematuria, intravesical immuno- or chemotherapy within 3 months prior to HAL administration (except for 1 immediate, postoperative intravesical instillation), known allergy to HAL or a similar compound and pregnancy.

The trial was approved by the local ethics committee and conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All subjects provided written informed consent.

2.2. Photosensitizer

HAL (Hexvix; Photocure ASA, Oslo, Norway) was supplied as powder and solvent for solution for intravesical use. 50 ml of a 16 mM (4 patients) or 8 mM HAL (13 patients) solution were instilled intravesically via a 12 Ch. catheter after drainage of residual urine, and the patients were encouraged to maintain the fluid for at least 1 hour prior to illumination.

2.3. Irradiation system

Bladder wall irradiation was performed using an incoherent white light source (T-Light; Karl Storz GmbH and Co. KG, Tuttlingen, Germany) tested in a preliminary feasibility study including intravesical 5-ALA application [8]. The light source comprised a 500 W short arc Xenon bulb emitting light in the visible spectrum from 380 to 700 nm. A total of 2 to 6 W could be transmitted through a single 1.5 mm diameter quartz fiber assembled into a 20 Ch. transurethral irrigation catheter (OptiMed GmbH, Ettlingen, Germany). This catheter was manufactured to suit the requirements of PDT in the following way: in a slightly lens-shaped lumen with a minimum diameter of 2.5 mm, the quartz fiber is inserted through a liquid-tight lock. Additionally, a connector for in-flow irrigation through the same lumen is available at the proximal end of the catheter. An optical scattering body mounted to the distal end of the quartz fiber enabled homogeneous light distribution towards the entire bladder wall. In-flow irrigation passed by this scattering rod and left the catheter sideways through a hole close to the catheter tip. On the opposite side, a hole was connected with a lumen to allow out-flow of irrigation fluid. A third lumen in the catheter served to inflate a blocking balloon with a diameter of 20 mm, ensuring the central placement of the scattering body within the bladder. Continuous irrigation with isotonic saline solution at body temperature was maintained during the entire irradiation procedure at a pressure sufficient to distend the bladder without folds. The bladder volume was determined by suprapubic ultrasound and controlled every 10 minutes. It was held steady over the irradiation time by synchronizing the fluid in- with the fluid out-flows.

After PDT, the treatment fiber was removed from the catheter and the output power measured at the bare ended fiber tip. The applied fluence rate was calculated based on the light power measured, considering the efficiency factor for the scattering body and the bladder surface area, which was determined from the filling volume under the assumption of a spherical bladder. The applied light dose was calculated as the product of fluence rate and irradiation time.

2.4. Treatment

Standard cystoscopy under white and blue light was conducted prior to each PDT course. Any papillary tumor seen at this point was resected prior to bladder irradiation. After PDT, the bladder was again inspected with blue light to assess the degree of photobleaching induced, with special attention at the bladder neck. Bladder wash cytology was to be performed at each visit. Each patient received 3 treatments with HAL-PDT 6 weeks apart (Fig. 1), using 1 to
2-hour instillation of 8 mM HAL (13 patients) or 16 mM HAL (4 patients) before white light irradiation. The first 14 patients treated had a target light dose of 100 J/cm². To investigate whether lowering the light dose could reduce possible side effects, the subsequent 3 patients had a target light dose of 25 J/cm² at the first PDT, 50 J/cm² at the second PDT and 100 J/cm² at the third PDT treatment. The 3 last patients also received intravesical instillation of local anaesthesia (50 ml lidocaine 2% for 30 minutes) instead of general anaesthesia.

2.5. Analysis and statistical methods

After PDT, patients were followed by regular cystoscopy every 3 months up to 21 months to assess time to recurrence. Patients with recurrence at any time during follow-up were taken out of the study and treated at the discretion of the investigator. Patient characteristics were described by means of descriptive statistics and frequency tables.

The safety endpoint was assessed from entry point until 3 months after the last PDT treatment. Reported adverse events (AEs) were coded according to the World Health Organization Adverse Reaction Terminology (WHO-ART). Furthermore, efficacy was assessed by cystoscopy, cytology, and histology, and was defined as the number of patients who were tumor-free at 6 (first assessment of efficacy), 9, or 21 months after initial PDT treatment. A 2-sided 95% confidence interval (CI) was calculated for the efficacy assessment.

3. Results

3.1. Patient characteristics

Seventeen patients, 6 women and 11 men between 44 and 86 years (mean 66.7 ± 12.1) were enrolled from March 2005 until August 2007. At study enrolment, 12 out of 17 patients (70.6%) had undergone a BCG treatment, 8 patients (47.1%) had been treated with intravesical chemotherapy, and 2 patients (11.8%) presented with no prior treatment. Regarding diagnoses, 2 patients presented with low-grade early recurrence within 6 months of local chemotheraphy or BCG, 14 patients with recurrent TaG3 and/or CIS, 1 patient with recurrent T1 non-eligible for cystectomy.

3.2. PDT treatment

The initial dosage was 16 mM HAL dissolved in 50 ml buffer. After the first 4 patients, the drug dose was changed to 8 mM HAL. The first 14 patients were intended for treatment with 100 J/cm²; median light doses for the first, second, and third PDT were 92.4, 102.5, and 94.0 J/cm², respectively. For the last 3 patients, a dose-escalating regimen was applied, with median light doses of 23.0, 51.0, and 106.0 J/cm² for the first, second, and third PDT treatment, respectively. Prior to PDT, positive PpIX-fluorescence was observed in all but 2 cases. In 10 cases, 1 or several papillary tumors were resected, but there were always flat fluorescent lesions left in these bladders. In 11 cases, a small probe excision from flat fluorescent lesions was taken. As positive fluorescence was present in most cases, a correlation with outcome was not considered useful. Subjectively, the overall area and contrast of fluorescence positivity was diminishing over the course of the 3 PDTs, but there was no attempt made to objectify this finding.

PDT was performed without any technical complications. Complete bleaching of the PpIX-fluorescence, as intended (Fig. 2), could be achieved in 43 of 45 PDT sessions with 100 J/cm², in 2 of 3 with 50 J/cm² at the second PDT and 100 J/cm² at the third PDT treatment. The 3 last patients also received intravesical instillation of local anaesthesia (50 ml lidocaine 2% for 30 minutes) instead of general anaesthesia.

3.3. Safety assessment

The most frequent body system for AEs was the lower urinary tract. Seventy-one AEs were reported in 15 (88.2%) patients (Table 1). Seven serious adverse events (SAEs) were reported in 4 (23.5%) patients. Two of these SAEs were considered related to the PDT treatment; 1 patient experienced severe irritative bladder/urgency syndrome, another patient experienced macroscopic hematuria, most probably caused by catheter insertion-related bleeding of prostate varices. These 2 patients had received 16 mM HAL and the drug dose was subsequently reduced to 8 mM. The remaining 5 SAEs were considered unrelated to the PDT treatment. No patient experienced bladder shrinkage, cutaneous photosensitization, or systemic side effects. All AEs occurred after the PDT treatment. Patients who only received local anaesthesia did not report more severe side effects than patients who were treated under general anaesthesia. A reduction in light dose did not result in notable changes in the number or severity of AEs reported. No
evidence of a cumulative effect of treatment on the incidence of AEs could be detected. There were no clinically meaningful changes from baseline in laboratory variables or vital signs. All symptoms reported in the urinary tract were transient and resolved completely. The mean duration of adverse events was 9.5 days.

3.4. Efficacy assessment

Of the 17 patients included, 9 (52.9%; 95% CI: 27.8–77.0) were tumor-free at 6 months, 4 (23.5%; 95% CI: 6.8–49.9) were tumor-free at 9 months, and 2 (11.8%, 95% CI: 1.5–36.4) were tumor-free after 21 months. One patient died of a heart attack after 18 months without bladder tumor recurrence. No data were available of 3 patients (Table 2).

4. Discussion

Clinical acceptance of bladder PDT has been limited by its complexity and side effects [19]. Dye lasers or diode lasers were most commonly used, and light was applied via isotropic fiber applicators, inserted into the bladder through the working channel of rigid cystoscopes. For the present study, a catheter-based light applicator, fed by a non-laser source was used to circumvent laser safety issues and to enable PDT treatments outside dedicated operation rooms.

The stiffness of the catheter was mainly determined by the quartz fiber within and allowed easy passage through the urethra. During irradiation, the bladder volume was kept constant by controlling the in- and out-flows with fine adjustment tap cocks. This required repetitive volumetric ultrasound measurements. These direct measurements allowed for the objective control of an unambiguously constant bladder volume and reliable light dosimetry. For a routine implementation of the procedure, however, these measurements could be replaced by other techniques; for example, an active control of in- and out-flows by electronic pump-systems or a passive pressure controlled device as suggested by Berger et al. [7].

With the use of white light, the phototoxic potential of PPIX and potential photoproducts might be exploited more efficiently than with a monochromatic laser light source. PPIX is excited most efficiently by violet light at 400 to 410 nm and with decreasing efficiency at 500 to 505, 535 to 540, 565 to 575, and 620 to 635 nm [8,20]. White light is therefore potentially more efficient in inducing the desired phototoxicity than red laser light. Due to the rapid photo-bleaching of the sensitizer, the requirements for light dosimetry are reduced to avoid an undertreatment. Undertreatment might potentially occur at areas of the bladder wall receiving low light intensities, e.g., at the bladder outlet. After instillation of 5-ALA, the bladder outlet is always fluorescence positive [21–23]. Thus, complete bleaching at

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**Table 1**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Number of patients* with AEs n = 17 (%)</th>
<th>Number of AEs, n = 128 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td>17 (100.0)</td>
<td>128 (100)</td>
</tr>
<tr>
<td>Most common AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Irritative bladder symptoms</td>
<td>15 (88.2)</td>
<td>12 (70.6)</td>
</tr>
<tr>
<td>-Urinary tract infection</td>
<td>5 (29.4)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>-Macrohematuria</td>
<td>1 (5.9)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>4 (23.5)</td>
<td>2 (11.8)</td>
</tr>
</tbody>
</table>

* One patient could have more than one AE.
Table 2

<table>
<thead>
<tr>
<th>Number of tumor-free patients</th>
<th>Assessment at 6 months</th>
<th>Assessment at 9 months</th>
<th>Assessment at 21 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>9</td>
<td>4</td>
<td>2*</td>
</tr>
<tr>
<td>Relative frequency</td>
<td>52.9%</td>
<td>23.5%</td>
<td>11.8%</td>
</tr>
<tr>
<td>95% CI</td>
<td>(27.8–77.0)</td>
<td>(6.8%–49.9%)</td>
<td>(1.5%–36.4%)</td>
</tr>
</tbody>
</table>

* One patient died after 18 months without recurrence.

PDT using hexaminolevulinate and a special flexible irradiation catheter system is technically feasible and might offer an alternative option in selected patients for the treatment of non-muscle-invasive intermediate and high-risk bladder cancer.

References


