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Original article

Follow-up of high-risk bladder cancer—Is it safe to perform fluorescence endoscopy multiple times in the same patient?

Maria Apfelbeck, M.D.*, Tobias Grimm, M.D., Alexander Kretschmer, M.D., Alexander Buchner, M.D., Birte-Swantje Schneevoigt, M.D., Friedrich Jokisch, M.D., Markus Grabbert, M.D., Gerald Schulz, M.D., Christian G. Stief, M.D., Ph.D., Alexander Karl, M.D.

Department of Urology, Ludwig-Maximilians-University of Munich, Munich, Germany

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Abstract

Purpose: As the use of fluorescence endoscopy is recommended today by different guidelines during the follow-up of high-grade non–muscle-invasive bladder cancer, the aim of this study is to analyze whether the multiple use of hexylaminolevulinate (HAL) for TUR-BT can be performed safely within the same patient over a time interval.

Methods: Data of patients diagnosed and treated with HAL-TUR-B at our institute between 2008 and 2013 were analyzed. Special interest was given to side effects observed during the instillation of the substance, on the whole day of the instillation and during the entire hospital stay. We focussed on side effects associated with the use of HAL, such as allergic reactions, urinary tract infections, photosensitization of the skin, and relevant changes in blood pressure.

Results: In the time between 2008 and 2013, 2480 HAL-TUR-BTs were performed in total at our institute. In 80 patients, HAL-TUR-BT was used at least 2 times, and on average 4 times (2–12 times). Only patients with multiple uses were included for our final analysis. We observed no allergizations in any of the treated patients. Minor side effects were urinary tract infections ($n = 4$), dysuria ($n = 4$), pollakisuria ($n = 9$), and bladder spasms ($n = 17$).

Conclusion: In our study cohort, the multiple use of HAL-TUR-BT within the same patient caused no major side effects or an induction of allergization against the substance. We, therefore, conclude that HAL-TUR-BT can be performed safely in the same patient during the follow-up of aggressive tumors as recommended by different guidelines today.

Keywords: Bladder cancer; Photodynamic diagnosis; Hexylaminolaevulinate; Allergic reaction

1. Introduction

Urothelial cell carcinoma of the bladder is classified into the group of non–muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer and is further classified into low- and high-grade tumors according to their grading. In approximately 75% of initially diagnosed cases [1], NMIBC (tumor stages: Ta, T1, and carcinoma in situ [CIS]) is detected. Among this group of NMIBC, there is a subgroup of high-risk tumors with a high potential of progression and even mortality [2]. CIS is among these high-risk cancers and appears as a velvety, reddish area of the bladder in white light (WL) cystoscopy and is sometimes difficult to distinguish from inflammatory lesions of the bladder.

The standard TUR-BT is performed using WL-cystoscopy. However, there is evidence that malignant lesions can be missed under WL conditions [3,4]. Therefore, new techniques for the visualization of bladder cancer have been developed. Hexylaminolevulinic acid (Hexvix in Europe, Cysview in the United States) is used to improve the diagnosis of bladder cancer—especially of flat lesions associated with high-grade tumors. Hexylaminolevulinate (HAL) is a derivate of 5-aminolaevulinic acid (ALA). After

* Corresponding author. Tel.: +49-894-4007-2649; fax: +49-894-4007-5644.
E-mail address: maria.apfelbeck@med.uni-muenchen.de (M. Apfelbeck).

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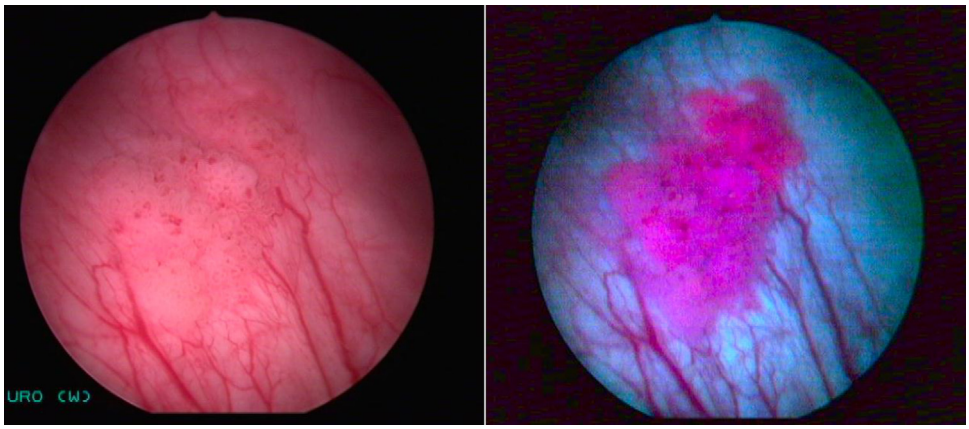

Fig. Papillary tumor under white light and blue light cystoscopy. (Color version of the figure available online.)

being absorbed by malignant cells, the acid is converted into the fluorescent substance protoporphyrin IX. The specific metabolism of cancer cells leads to an accumulation of protoporphyrin IX in tumor tissue [5,6]. The Fig. shows a papillary tumor under WL and blue light conditions. Under blue light, the tumor appears in red.

The photosensitizer HAL is instilled into the bladder via a Foley catheter before the performance of cystoscopy. Using blue light (345–475 nm), tumorous lesions can be detected by their reddish fluorescence (Fig.). This facilitates the diagnosis of flat aggressive carcinoma lesions and high-grade papillary tumors.

Kausch et al. [2] and Mowatt et al. [4] have shown that fluorescence cystoscopy has a higher sensitivity than WL-cystoscopy at patient (92% vs. 71%) and biopsy—level (93% vs. 65%). Furthermore, fluorescence-guided biopsy is more sensitive in detecting CIS than a random biopsy under WL conditions [2,4], and it increases the detection rate of tumor lesions regardless of risk group and decreases the overall recurrence rate [7].

Therefore, the European guidelines recommend the use of HAL when CIS or a high-grade tumor is suspected (e.g., positive cytology, and recurrent tumor with previous history of high-grade lesion) [8]. Although many studies show the efficacy of photodynamic diagnosis (PDD) in the detection of high-grade tumors [3,4], none describes the side effects of PDD when used several times in the same patient over time. The in situ use of pharmaceuticals can, for example, lead to allergic reactions, such as erythema of the skin, pruritus, or blistering. An allergy is defined as an overreaction of the immune system. Before an allergic reaction can occur, a sensitization (formation of IgE-antibodies) with the allergen has to take place. Symptoms of an allergy are not possible before the second exposition to the same substance. This is of special interest for the multiple use of HAL, especially when HAL is used in the follow-up of patients with high-risk bladder cancer. Different studies are published analyzing possible side effects after the intravesical instillation of HAL, but using HAL only for the first time [9–14]. There is only 1 case report in the literature describing a possible allergic reaction after the intravesical instillation of HAL [15]. But there are none focussing on allergic reaction and other side effects, when using HAL several times within the same patient.

The aim of this study is to evaluate possible side effects during or after the instillation of HAL in patients who already underwent at least 1 PDD using HAL in the past. We were especially interested if the multiple use of PDD can induce allergic reactions.

2. Materials and methods

Between 2008 and 2013, 2,480 transurethral resections of the bladder (TUR-BT) using HAL at our institute have been performed due to bladder cancer; 80 patients, who underwent TUR-BT more than once using HAL, have been included in our retrospective analysis.

All included patients had been instilled with HAL into the bladder at least 1 hour before PDD and TUR-BT took place.

TUR-BT was performed using a rigid cystoscope (26 Chr. Storz) using white and blue light in the same patient. Biopsies of the urethral mucosa were taken, or TUR-BT was performed for histological examination. For each patient, hospital charts were reviewed and entered into our institute's database. Data were collected for each patient from the time of admission to the hospital until the patient's discharge for each and every hospital stay over a duration of time.

Every patient received a transurethral catheter at the end of the TUR-BT. Furthermore, all patients received a perioperative antibiotic prophylaxis, minimum for 1 day and maximum until the discharge from the hospital. We focused on possible side effects during the actual instillation of HAL, during the day of the instillation, and over the entire hospital stay. To determine side effects, we looked for symptoms that indicated urinary tract infection (UTI), dysuria, pollakisuria as well as micro- and gross hematuria. In addition, we also assessed effects on routinely collected