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Photodynamic diagnosis of bladder cancer: Initial experience of a single UK centre

S.O. Osaghae[1,*], **D.T.L. Turner**

Department of Urology, Pilgrim Hospital, Boston, Lincolnshire, UK

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Hexvix;
Blue light cystoscopy (BLC);
White light cystoscopy (WLC)

Abstract
Objectives: To describe the introduction and evaluate efficacy of photodynamic diagnosis with Hexvix for detecting tumours and abnormal mucosal lesions during transurethral resection of bladder tumour (TURBT).
Subjects and methods: Prospective study of consecutive eligible patients who underwent TURBT with aid of Hexvix-guided cystoscopy in a single District General Hospital (NHS Trust in England).
The participants selected were patients suspected to have bladder cancer or enlisted to undergo TURBT.
The main outcome measures were the number of tumours or abnormal mucosal lesions that were missed by white light cystoscopy (WLC) but detected by Hexvix, blue light cystoscopy (BLC).
Results: A total of 63 patients (39 males and 24 females; mean age 74 years; age range, 35–88 years) met study criteria. 15 were excluded: in 6 intra-vesical Hexvix was retained for <1 h, and in 4, TURBT was delayed by >1 h; of the remaining 53 patients, 5 were excluded for technical reason, failure of fluorescence. Seventy five lesions were detected in the remaining 48 patients. Of these, 51 (68%) were detected by WLC and BLC both. BLC detected additional 24 (32%) lesions that were missed by WLC. Of these lesions, 15 (20%) were cancer and 9 (12%) were inflammation or dysplasia.
Conclusion: BLC with Hexvix was easily introduced into a Bladder cancer management protocol and well tolerated by most patients. BLC increased diagnostic accuracy of cystoscopy during TURBT, although some of the lesions it detected were false positive.

* Corresponding author at: Department of Urology, Watford General Hospital, Vicarage Road, Watford WD18 0HB, UK.
E-mail address: sosaghae@aol.com (S.O. Osaghae).
[1] Current Institution: Watford General Hospital, Watford, Hertfordshire, UK.
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Introduction

Over 10,000 people are diagnosed annually with bladder cancer (BC) in the United Kingdom, where it is the 7th most common cancer [1]. Non-muscle-invasive BC (NMIBC) accounts for 75–85% of all newly diagnosed BC cases [2]. The 5-year survival rate of patients with bladder cancer confined to the mucosa (TaT1 NMIBC), is 80–90% [3]. About 25–75% will develop recurrent disease [3,4]. Many progress to muscle invasive BC (MIBC) or metastatic disease [5]. Of the TaT1 NMIBC recurrences, 25–60% may be due to incompleteness of TURBT because white light cystoscopy (WLC) does not visualize all tumour-bearing sites [6,7]. Indeed, check cystoscopies detect residual or recurrent disease in about 55% of cases [6–9].

The limitations of WLC led to the development of Photodynamic diagnosis, PDD with 5-Aminolevulinate (5-ALA) and Hexaminolevulinic acid (HAL; trade name Hexvix) respectively. It has been reported to improve recurrence-free survival (RFS) of patients with bladder cancer [7–18]. International expert panels have also produced guidelines for PDD with Hexvix, namely diagnosis of NMIBC that has not yet been subjected to TURBT, follow-up of patients with NMIBC, additional testing of patients with positive urine cytology but negative WLC, follow-up of patients with multifocal disease and suspected carcinoma *in situ* (CIS) [19,20]. A recent study by the Health Technology Assessment programme of the National Health Service of the United Kingdom came to three conclusions. First, PDD detects BC more sensitively but less specifically than WLC and is better at detecting more aggressive and higher risk tumours, including CIS. Second, compared to WLC, when PDD is used in the initial TURBT, fewer residual tumours are found by check cystoscopy and the RFS is longer. Third, it is not clear whether PDD at TURBT reduces tumour recurrence and progression in the long term better than WLC. Nevertheless, PDD provides additional benefits at a cost that society may be willing to pay [21]. The present study aimed to provide preliminary evidence to justify the routine use of Hexvix in our hospital and its introduction in all the Trust's hospitals.

Subjects and methods

PDD with Hexvix

Hexvix and 5-ALA are fluorochromes and haem precursors that are administered through a urethral catheter into the bladder to aid tumour detection on the basis of fluorescence [16,22,23]. They accumulate in tumour cells that metabolize them stepwise into first porphyrin and then protoporphyrin IX which generates a purplish fluorescence. This is detected as blue by D-light (Xenon lamp) by a specially developed light cable and special filter mounted on the cystoscope eye-piece which has dual blue and white light functions. This allows cystoscopic visualization of the tumours under white and blue light respectively (Fig. 1).

The chemical structure of Hexvix and 5-ALA are very similar: Hexvix is essentially 5-ALA plus a lipophilic hexyl moiety. However, Hexvix has four times the fluorescent power of 5-ALA. Hence, although 5-ALA was developed first and is available for oral and intravesical use, it is often replaced by Hexvix, which is currently only available for intravesical instillation. Hexvix is supplied as a powder that is dissolved in a 50 ml buffer solution before instillation into the bladder. The patient is expected to retain it within the bladder for at least 1 h prior to TURBT (by contrast, 5-ALA must be retained for 2–3 h before TURBT). Hexvix accumulates in cancerous bladder tissue and after illumination with blue light cystoscopy (BLC), a clearly visible purplish fluorescence is observed (Fig. 1a).

Hexvix was developed by Photo cure, ASA, Oslo, Norway and has been available, to UK Urologists, since about 2003.

Prospective trial

This prospective study of 63 consecutive patients with history of BC was performed between January 2009 and November 2010. The patients were included either because they had new presentation with bladder tumour, recurrent BC, positive urine cytology but a negative WLC or suspected CIS. Study approval was obtained from the Hospital Clinical Governance Committee. All patients consented to PDD with Hexvix.

Technique

Briefly, 85 mg of Hexvix was dissolved in 50 ml solvent and instilled into the bladder *via* a urethral catheter 1 h before TURBT. Patients

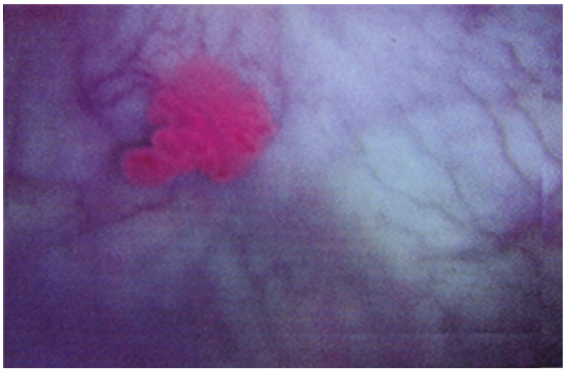

Figure 1 Blue light chemistry and tumour detection.