Efficacy and Safety of Blue Light Flexible Cystoscopy with Hexaminolevulinate in the Surveillance of Bladder Cancer: A Phase III, Comparative, Multicenter Study

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Abbreviations and Acronyms

AE = adverse event
BCG = bacillus Calmette-Guérin
BL = blue light
BLC = BL cystoscopy
BLFC = flexible BLC
CIS = carcinoma in situ
HAL = hexaminolevulinate
PDD = photodynamic diagnosis
PUNLMP = papillary urothelial neoplasm of low malignant potential
TURB = transurethral bladder resection
WLC = white light cystoscopy
WLFC = flexible WLC

Purpose: We compared blue light flexible cystoscopy with white light flexible cystoscopy for the detection of bladder cancer during surveillance.

Materials and Methods: Patients at high risk for recurrence received hexaminolevulinate intravesically before white light flexible cystoscopy and randomization to blue light flexible cystoscopy. All suspicious lesions were documented. Patients with suspicious lesions were referred to the operating room for repeat white and blue light cystoscopy. All suspected lesions were biopsied or resected and specimens were examined by an independent pathology consensus panel. The primary study end point was the proportion of patients with histologically confirmed malignancy detected only with blue light flexible cystoscopy. Additional end points were the false-positive rate, carcinoma in situ detection and additional tumors detected only with blue light cystoscopy.

Results: Following surveillance 103 of the 304 patients were referred, including 63 with confirmed malignancy, of whom 26 had carcinoma in situ. In 13 of the 63 patients (20.6%, 95% CI 11.5–32.7) recurrence was seen only with blue light flexible cystoscopy ($p < 0.0001$). Five of these cases were confirmed as carcinoma in situ. Operating room examination confirmed carcinoma in situ in 26 of 63 patients (41%), which was detected only with blue light cystoscopy in 9 of the 26

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(34.6%, 95% CI 17.2–55.7, p <0.0001). Blue light cystoscopy identified additional malignant lesions in 29 of the 63 patients (46%). The false-positive rate was 9.1% for white and blue light cystoscopy. None of the 12 adverse events during surveillance were serious.

Conclusions: Office based blue light flexible cystoscopy significantly improves the detection of patients with recurrent bladder cancer and it is safe when used for surveillance. Blue light cystoscopy in the operating room significantly improves the detection of carcinoma in situ and detects lesions that are missed with white light cystoscopy.

Key Words: bladder neoplasms; neoplasm recurrence, local; carcinoma in situ; cystoscopy; optical imaging

Approximately 75% of bladder cancers present as nonmuscle invasive disease, which is treated initially with TURB. Recurrence is common, often due to incomplete resection as there are inherent limitations in identifying all malignant lesions with WLC alone.[1] Residual tumor can be found in 30% to 44% of resected cases up to 8 weeks after surgery[2–4] and the rate may reach 70% for high grade tumors.[5,6]

Due to the risk of recurrence and progression patients require regular surveillance cystoscopies, usually every 3 to 6 months.[7] This is routinely performed with WLFC using local anesthesia in the office setting.

Diagnostic techniques based on photoactive porphyrins such as HAL aim to improve the detection and resection of nonmuscle invasive bladder cancer. These agents accumulate preferentially in neoplastic tissue, where they induce an accumulation of protoporphyrin IX, which fluoresces when exposed to blue light between 375 and 440 nm.[8,9] This enhances the demarcation between normal and cancerous tissue, enabling improved detection of exophytic tumors and CIS.[10–14] The detection of additional tumors could have a profound impact on future treatment plans while enhanced visualization allows for more complete resection during TURB.[11]

Growing evidence demonstrates the ability of BLC with HAL to increase tumor detection[15] and improve resection during TURB with subsequent decreased cancer recurrence and cost of care.[11,16–20] In Europe for approximately 3 years a flexible PDD videoscope, the D-Light C PDD Flexible Videoscope System (Karl Storz Endoscopy-America, El Segundo, California) with a chip on the tip has been used with HAL. The latter is marketed as Hexvix® in Europe and as Cysview® in the United States. However, to our knowledge no formal clinical study has yet been performed to determine the improved detection of bladder cancer during surveillance using the flexible PDD cystoscope for BLFC with HAL.

We hypothesized that BLC using a flexible cystoscope would have clinical benefits over white light in patients undergoing office based surveillance. The main aim of this prospective, multicenter, phase III study was to compare BLFC with HAL to WLFC in the detection of bladder cancer during surveillance.

MATERIALS AND METHODS

Study Design

This prospective, open label, comparative, within patient, controlled, phase III study was done at 17 centers across the United States. It was performed in accordance with Good Clinical Practice, including ICH (International Conference on Harmonisation) Harmonised Tripartite Guideline E6 and the Declaration of Helsinki as well as title 21 of the United States Code of Federal Regulations, Parts 50, 56 and 312. Written approval was obtained from the relevant institutional review board at each study site and all patients provided fully informed written consent before enrollment.

Patients

Patients with a history of multiple, recurrent or high grade bladder tumors were eligible if they had a tumor that was histologically confirmed by TURB or previous surveillance cystoscopy. Patients who had previously received BCG immunotherapy or intravesical chemotherapy were included in analysis as long as 6 weeks had elapsed since the last treatment.

Surveillance Examination Process

Following screening and enrollment the patients had the first surveillance visit, during which a urine sample was obtained for cytology. After the bladder was emptied HAL in phosphate buffered saline solution (50 ml of 8 mM solution) was instilled in the bladder of all patients and retained for 1 to 3 hours. Patients received intraurethral anesthesia according to institutional practice. After bladder evacuation the number, size and appearance of all suspected malignant lesions were recorded with white light using the described cystoscopy system.

Following WLFC a sealed randomization envelope was opened to see whether the patient would continue in the study. Randomization was done to ensure that a thorough inspection would be made with white light. Patients randomized to continue were inspected again by the same