Hexaminolevulinate Guided Fluorescence Cystoscopy Reduces Recurrence in Patients With Nonmuscle Invasive Bladder Cancer

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Purpose: We assessed the impact that improved detection of nonmuscle invasive bladder cancer with hexaminolevulinate fluorescence cystoscopy may have on early recurrence rates.

Materials and Methods: This prospective, randomized study enrolled 814 patients suspected of having bladder cancer at increased risk for recurrence. All patients underwent white light cystoscopy and mapping of lesions, followed by transurethral resection of the bladder when indicated. Patients in the fluorescence group also received intravesical hexaminolevulinate solution at least 1 hour before cystoscopy to induce fluorescence of cancerous lesions, and underwent additional inspection with blue light before and after transurethral resection of the bladder. Adjuvant intravesical therapy was based on risk. Followup cystoscopy at 3, 6 and 9 months was conducted with white light.

Results: Detection was performed as a within patient comparison in the fluorescence group. In this group 286 patients had at least 1 Ta or T1 tumor (intent to treat). In 47 patients (16%) at least 1 of the tumors was seen only with fluorescence ($p = 0.001$). During the 9-month followup (intent to treat) there was tumor recurrence in 128 of 271 patients (47%) in the fluorescence group and 157 of 280 (56%) in the white light group ($p = 0.026$). The relative reduction in recurrence rate was 16%.

Conclusions: Hexaminolevulinate fluorescence cystoscopy significantly improves the detection of Ta and T1 lesions and significantly reduces the rate of tumor recurrence at 9 months.

Key Words: urinary bladder neoplasms, 5-aminolevulinic acid hexyl ester, fluorescence, cystoscopy, recurrence

Abbreviations and Acronyms

AE = adverse event
ALA = aminolevulinic acid
BCG = bacillus Calmette-Guérin
CIS = carcinoma in situ
HAL = hexaminolevulinate
ITT = intent to treat
PPS = per protocol set
TURB = transurethral resection of the bladder

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EVEN when performed by experienced urologists, cystoscopy can miss clinically important papillary tumors and CIS. Repeat TURB performed only a few weeks after the initial resection demonstrates that incomplete resection is common.[1] Residual tumor is found in 30% to 44% of patients resected up to 8 weeks after the original surgery,[2–4] and the rate can be as high as 70% for high grade tumors.[5,6]

Fluorescence cystoscopy uses photoactive compounds to enhance the visual demarcation between normal

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and neoplastic tissue. Endogenous ALA is a natural precursor of the photoactive intermediate protoporphyrin IX. Intravesical hexaminolevulinic acid, a hexyl ester of 5-ALA, induces accumulation of protoporphyrin IX in malignant cells, which fluoresces when exposed to light between 375 and 440 nm,[7,8] enabling the detection of more exophytic tumors and CIS than white light cystoscopy.[9–13] In this international study we assessed the impact that improved detection of bladder cancer with hexaminolevulinate cystoscopy has on tumor recurrence.

METHODS

Patients

A total of 28 centers (19 in the United States and Canada, and 9 in Europe) enrolled patients with suspected Ta and/or T1 bladder cancer on the basis of outpatient cystoscopy. Eligible patients were at increased risk for recurrence based on the presence of more than 1 initial or recurrent papillary bladder tumor or recurrence within 12 months of a previous bladder cancer. Patients with gross hematuria, porphyria and those who received BCG or multiple instillation chemotherapy in the 3 months before initial TURB were excluded from the study. The trial was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice and the Declaration of Helsinki (September 10, 2004 version). All patients provided written informed consent.

Hexaminolevulinate Treatment

Hexaminolevulinate (Photocure, Oslo, Norway) was supplied as 85 mg powder for reconstitution in 50 ml phosphate buffered saline. The solution was instilled into the bladder and was to be retained for 1 hour. A xenon light source (D-Light C system, Karl Storz Co, Tüttlingen, Germany) was used for blue and white light cystoscopy.

Randomization and Treatment Protocol

Randomization was performed centrally, and was stratified for patients presenting with initial and recurrent bladder cancer. Patients in the white light group underwent cystoscopy and mapping of bladder lesions followed by TURB with white light (fig. 1).

In the fluorescence cystoscopy group lesions were first mapped using white light cystoscopy. Immediately after mapping a second randomization was performed to ensure that a thorough inspection was performed with white light. Patients randomized to discontinue the study were excluded from further efficacy analyses but were monitored for AEs. Patients randomized to continue in the study underwent bladder mapping again using blue light. They then underwent TURB using blue light to evaluate the completeness of the resection (fig. 1).

At centers with no prior experience with fluorescence cystoscopy the first 5 patients enrolled were considered training patients. They were not randomized into the study, they received fluorescence cystoscopy and they were only included in the safety analysis.

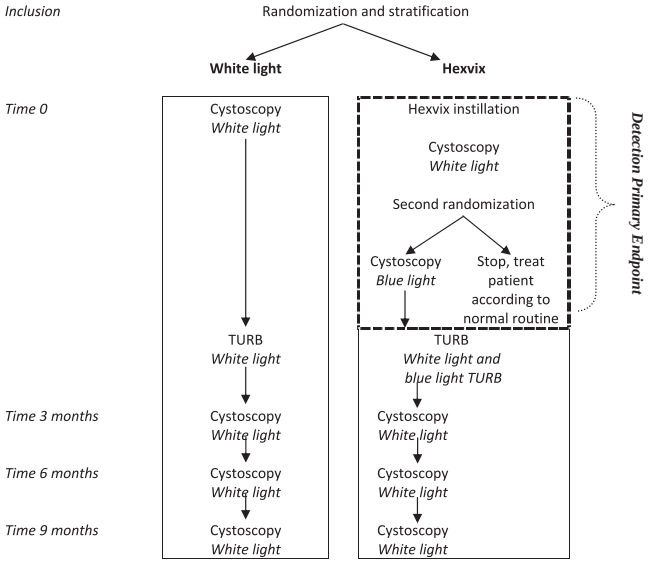

Figure 1. Study flow

For all patients continuing in the study all exophytic lesions were resected and all suspicious lesions were biopsied. These biopsies were analyzed by a local pathologist and by a panel of central pathologists blinded to the decision of the local pathologist. The central pathology panel consensus read was used as the standard of truth for the detection end points. For the recurrence end point local pathology was used because all clinical decisions were based on local pathology.

Flat lesions were graded according to the WHO/International Society of Urologic Pathology 1998 consensus classification of urothelial (transitional cell) neoplasms of the bladder[14] and according to McKenney et al,[15] while papillary lesions were graded according to WHO 1973.[16]

Patients with high grade bladder cancer, T1 or CIS according to local pathological examination received intravesical BCG unless contraindicated. Other intravesical therapy was not permitted. Only those patients with histologically confirmed Ta or T1 tumors based on the diagnosis of the local pathologist entered the followup phase of the study. Cystoscopy with white light was performed at 3, 6 and 9 months following initial resection or until recurrence. Recurrence was confirmed histologically.

Analyses and Statistical Methods

The study assessed the effects of fluorescence cystoscopy on the detection of nonmuscle invasive bladder tumors and on bladder cancer recurrence. The analysis populations are shown in table 1. The primary detection end point was the proportion of patients with histologically confirmed Ta or T1 tumors in the fluorescence cystoscopy group who had at least 1 additional histologically confirmed Ta or T1 tumor detected with blue but not with white light.

Secondary end points included the proportion of patients in the fluorescence cystoscopy group who had additional CIS lesions detected with blue light. For analysis of