Early detection of urothelial premalignant lesions using hexaminolevulinate fluorescence cystoscopy in high risk patients

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Abstract

Background: To evaluate fluorescence cystoscopy with hexaminolevulinate (HAL) in the early detection of dysplasia (DYS) and carcinoma in situ (CIS) in select high risk patients.

Methods: We selected 30 consecutive bladder cancer patients at high risk for progression. After endoscopic resection, all patients received (a) induction BCG schedule when needed, and (b) white light and fluorescence cystoscopy after 3 months. HAL at doses of 85 mg (GE Healthcare, Buckinghamshire, United Kingdom) dissolved in 50 ml of solvent to obtain an 8 mmol/L solution was instilled intravesically with a 12 Fr catheter into an empty bladder and left for 90 minutes. The solution was freshly prepared immediately before instillation. Cystoscopy was performed within 120 minutes of bladder emptying. Standard and fluorescence cystoscopy was performed using a double light system (Combilight PDD light source 5133, Wolf, Germany) which allowed an inspection under both white and blue light.

Results: The overall incidence was 43.3% dysplasia, 23.3% CIS, and 13.3% superficial transitional cell cancer. In 21 patients, HAL cystoscopy was positive with one or more fluorescent flat lesions. Of the positive cases, there were 4 CIS, 10 DYS, 2 association of CIS and DYS, 4 well-differentiated non-infiltrating bladder cancers, and 1 chronic cystitis. In 9 patients with negative HAL results, random biopsies showed 1 CIS and 1 DYS. HAL cystoscopy showed 90.1% sensitivity and 87.5% specificity with 95.2% positive predictive value and 77.8% negative predictive value.

Conclusion: Photodynamic diagnosis should be considered a very important tool in the diagnosis of potentially evolving flat lesions on the bladder mucosa such as DYS and CIS. Moreover, detection of dysplastic lesions that are considered precursors of CIS may play an important role in preventing disease progression. In our opinion, HAL cystoscopy should be recommended in the early follow-up of high risk patients.
might be done by identification of a known precursor of CIS called severe dysplasia (DYS) [4,5]. Dysplasia is often located in normal-appearing bladder mucosa and can be easily missed under standard white-light (WL) cystoscopy [6]. Voided-urine cytology has proven useful as a non-invasive adjunct in the detection of CIS, although its sensitivity in the detection of DYS may be questionable [7,8].

Several investigators have used photodynamic agents to detect dysplastic urothelium [9,10]. Zaak et al previously concluded that 5-aminolevulinic acid (5-ALA) provided the most efficient diagnostic agent for patients with flat, high-risk urothelial lesions (CIS and DYS) compared with WL cystoscopy and cytology [11]. In our study, we used a recently introduced, more lipophilic ester of 5-ALA, hexaminolevulinate (HAL) to study DYS and CIS, and compared the detection rate with this agent to that of classic WL cystoscopy and fluorescence cystoscopy in select high risk patients.

Materials and methods

Between March 2007 and February 2008, 30 consecutive bladder cancer patients at high risk for progression were selected. Patients if needed started a BCG induction schedule within 30 days (once weekly for 6 weeks). The following WL and HAL cystoscopy control was performed after 3 months in order to minimize the likelihood of false positives [12,13]. Patients with porphyria, gross haematuria, acute urinary tract infection, multi-drug allergies, and women not on adequate contraceptive measures or who were breast feeding were excluded [14].

HAL at doses of 85 mg (GE Healthcare, Buckinghamshire, United Kingdom) dissolved in 50 ml of solvent to obtain an 8 mmol/L solution was instilled intravesically with a 12Fr catheter into an empty bladder and left for 90 minutes. The solution was freshly prepared immediately before instillation. Cystoscopy was performed within 120 minutes of bladder emptying as described below.

The purpose of preliminary WL cystoscopy was to identify and note any exophytic lesions and suspicious areas in the bladder chart. Subsequently, under blue light cystoscopy, we aimed to determine the number and location of all fluorescing areas on the same bladder chart. In patients without suspicion, 5 random biopsies were taken from normal appearing urothelium.

All biopsies and resected materials were analyzed by a single pathologist blinded to the fluorescence cystoscopy results. Lesions were staged and graded according to the 2004 WHO classification [15].

Safety assessments, including physical examinations, vital signs, and blood sampling for hematology and biochemistry were performed at baseline and again 24 hours after HAL instillation. All spontaneously reported and observed adverse events were documented during the hospital stay. Patients were followed for roughly 10 days until the consultation of their histologic results and were interviewed for any adverse effects after hospital discharge.

Categorical data were examined by chi-square test, while continuous variables were evaluated by the t-test. Specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with the usual mathematical formulas.

Results

Of the 30 patients, 24 were males and 6 were females. Their mean age was 67 (SD, 7.8; range, 46-76) years. For 11 patients, high risk transitional cancer was the first episode while in the remaining patients high risk episode was recurrent. (range, 2-11 resections; average 2.8 resections). In all patients, WL cystoscopy was negative. Urinary cytology was positive in 9 patients and suspected in 4 cases.

The overall incidence of DYS was 43.3% (13/30), CIS was 23.3% (7/30), and superficial transitional cell cancer was 13.3% (4/30). Disease-free follow-up occurred in 26.7% (8/30) of patients. In 21 patients, the HAL cystoscopy was positive, with one or more fluorescing flat lesions present (mean ± SD, 2.7 ± 1.4; range 1-5). The positive cases consisted of 4 CIS, 10 DYS, and 2 associations of CIS and DYS, well-differentiated superficial bladder cancer non-infiltrating to the lamina propria in 4 cases, and chronic cystitis in 1 case. In 9 patients with negative results by HAL, the 6 random biopsies showed one case each of CIS and DYS. HAL cystoscopy showed 90.1% sensitivity (95% CI, 0.53-0.87) and 87.5% specificity (95% CI, 0.47-0.99) and 95.2% PPV (95% CI, 0.74-0.99) and 77.8 NPV (95% CI, 0.40-0.96). CIS and DYS were both visible as a brilliant-red, well-limited fluorescence area in contrast with the normal adjacent urothelium.

HAL fluorescence cystoscopy was well tolerated and no unexpected events were reported.
Discussion

Bladder cancer risk categories are based on clinical and histopathologic parameters such as number of tumours, tumour size, prior recurrence rate, T category, presence of concomitant CIS, and tumour grade [16,17]. Among these, CIS is considered an important risk factor for disease progression because specific survival is heavily affected by the presence of CIS alone or associated with papillary superficial bladder cancer and non papillary T1 tumours [18]. So it should be necessary an earlier diagnosis when mucosal changes are still precursor of CIS. DYS is considered an epithelial abnormality appearing as a flat lesion on the bladder mucosa and a precursor of CIS [19]. This premalignant lesion might have important implications in the early diagnosis of bladder cancer progression. Several recent studies have shown that concomitant or single DYS is associated with a considerable risk for disease progression [20-22]. However, diagnosis is very difficult because, in the early stages, both lesions are indistinguishable from the normal-appearing bladder mucosa [6] and urine cytology testing might not be sufficiently sensitive [23].

The situation can be significantly improved with the use of photo sensitizers, e.g. 5-ALA or HAL, which can be safely administered intravesically and make these flat lesions visible within an otherwise normal bladder mucosa. Our results confirm the advantage in the diagnosis of potentially evolving flat lesions (DYS and CIS) on the bladder mucosa examined by photodynamic, rather than classic WL, cystoscopy. A real benefit was shown in the diagnosis of early papillary superficial bladder tumours that were not yet visible, confirming previous observations [24-28].

Regarding dysplasia, in a previous study, Zaak et al. concluded that photodynamic diagnosis using 5-ALA was an efficient diagnostic technique for patients with flat, high-risk urothelial lesions compared with classic WL cystoscopy and cytology [11]. In our study, we used HAL, a potent ester of aminolevulinic acid, that provides better selectivity, brighter fluorescence, and requires a shorter instillation time [29,30].

Another point of discussion is the incidence of DYS and CIS, which was 43.3% and 23.3%, respectively, in our study. This means that 66.6% of our patients had a potential evolving flat lesion. In the absence of photodynamic diagnosis, the incidence of such lesions would have been only 6.7%. These results suggest the careful consideration of all therapeutic possibilities, beginning with the careful endoscopic resection, as well as the therapeutic effect of immunoprophylaxis in these high risk patients. Because bladder cancer is often multicentric, particularly when it is of high grade, a standard WL resection might miss invisible tumours. Moreover, a BCG induction schedule might be not sufficient to treat these lesions making treated indeed during maintenance schedule. However, the detection rate of these otherwise undiagnosed lesions is higher with photodynamic screening.

The limitations of this study are the small number of patients included. However, we feel that this limitation is balanced by the highly selected series.

Further studies are needed to determine whether this important and not inexpensive diagnostic tool must be reserved for primary or secondary look resections of high risk patients and if the improvement in the rate of detection of flat lesions in the follow-up may improve the use of additional treatment and the prognosis of these patients.

Conclusions

Photodynamic diagnosis should be considered a very important tool in the diagnosis of potentially evolving flat lesions on the bladder mucosa such as DYS and CIS. Moreover, detection of dysplastic lesions that are considered precursors of CIS may play an important role in preventing disease progression. In our opinion, HAL cystoscopy should be recommended in the early follow-up of high risk patients.

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Authors’ contributions
SB has conceived the study and participated in its draft and design. MR has participated in its design and draft. BL has carried out the histological analysis. LN has participated in its revision. MG has conceived the study and participated in its design and coordination. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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