Current Urology Reports (2020) 21: 19
https://doi.org/10.1007/s11934-020-0966-5

UROTHELIAL CANCER (S DANESHMAND, SECTION EDITOR)

Blue Light Cystoscopy: Indications and Outcomes

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Published online: 4 April 2020

Abstract

Purpose of Review It has been firmly established that hexaminolevulinate-assisted blue light cystoscopy (HAL-BLC) reduces cancer recurrence rates. This review explores the impact of HAL-BLC on other meaningful outcomes in patients with bladder cancer, including disease progression, and earlier detection of disease at the time of surveillance cystoscopy.

Recent Findings A randomized clinical trial confirmed earlier implementation of HAL-BLC at the time of surveillance cystoscopy increased identification of cancerous lesions, including those of high grade, when compared with white light cystoscopy. In addition, the evidence is evolving that the use of HAL-BLC at the time of endoscopic treatment of high-risk tumors may lead to lower rates of progression to muscle invasion, and this in part may be due to better risk stratification leading to changes in treatment plan.

Summary The clinical contexts for the use of HAL-BLC are broader than prior knowledge. It is also becoming more clear that the positive impact of HAL-BLC is likely more than just reducing cancer recurrence rates, and patients would benefit from the technology at many time points in the management and follow-up of their disease.

Keywords Non-muscle invasive bladder cancer · Hexaminolevulinate · Blue light cystoscopy · Surveillance cystoscopy · Enhanced cystoscopy

Introduction

It is estimated that more than 81,000 individuals in the USA will be diagnosed with bladder cancer in the coming year, and 75% of the cases will be staged as non-muscle invasive bladder cancer (NMIBC) [1]. At least half of these individuals will develop a recurrent bladder tumor and even more concerning 5–25% of recurrences eventually progress to muscle-invasive bladder cancer (MIBC) [2–5]. Reliable visualization of bladder tumors is crucial to the success of curative intent transurethral resection of bladder tumor (TURBT). However, developments in technology have irrefutably determined that *carcinoma* in situ and other low and high grade flat or subtle papillary lesions are often not visualized by standard white light cystoscopy [6–9]. These initial studies suggested that TURBT exclusively dependent upon white light cystoscopy has the potential to impact patient outcomes in a negative manner.

A number of studies have consistently confirmed that the addition of fluorescence-assisted blue light cystoscopy to white light cystoscopy leads to better visualization of bladder tumors at the time of TURBT [6–9]. The procedure is dependent upon the intravesical administration of the heme precursor, hexaminolevulinate (HAL; which is known as Cysview in the USA and Hexvix in Europe). The administration of HAL results in preferential accumulation of protoporphyrin IX and other photoactive porphyrins in the mitochondria of neoplastic tissue that fluoresce red when exposed to blue light between 375 and 440 nm [10, 11]. Importantly, several studies confirm that better visualization of bladder tumors leads to the desired clinical benefit of reducing tumor recurrences suggesting a better quality TURBT when HAL-assisted blue light cystoscopy (BLC) is added to white light cystoscopy [12–15]. Many of these studies were included in a meta-analysis that used raw patient data, and the results were presented as within-patient comparison for tumor detection and between-patient comparison for tumor recurrence. The meta-analysis determined that white light cystoscopy missed 24.9% of Ta and T1 tumors and 26.7% of *carcinoma* in

This article is part of Topical Collection on *Urothelial Cancer*

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situ (CIS) tumors [16]. HAL-assisted BLC was associated with a 24% lower risk of recurrence at 12 months compared with white light cystoscopy alone (35 versus 45%; risk ratio 0.76; 95% confidence interval [CI], 0.63–0.92; $P = 0.006$). The observed benefit was independent of tumor risk category (i.e., intermediate or high risk) or whether the tumor was primary or recurrent NMIBC.

It is important to emphasize that blue light cystoscopy should be used in combination with white light cystoscopy to maximize the sensitivity of tumor detection. In a multicenter study of 311 patients with known or suspected NMIBC, HAL-BLC missed 9% of tumors seen by white light cystoscopy including a T1 bladder cancer. In the same study, HAL-assisted BLC detected at least one additional tumor compared with white light in 29% of patients and detected at least one additional T1 cancer in 15% of patients [8]. The study emphasizes the importance of the complementary benefit of using both blue and white light cystoscopy in the same patient to maximize benefit. Based on our own personal experience with HAL-assisted BLC, it should be recognized, although uncommon, that it is possible that a patient with a positive cytology has both a normal blue and white light cystoscopy but random bladder biopsies detect the presence of *carcinoma* in situ. Therefore, neither modality alone nor combined has perfect sensitivity for bladder cancer detection.

The high-level evidence supporting the use of HAL-BLC at the time of TURBT is further supported by the American Urological Association (AUA)–Society of Urologic Oncology (SUO) guidelines for managing NMIBC that states "in a patient with NMIBC, a clinician should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence. (Moderate Recommendation; Evidence Strength: Grade B)" [17]. Similarly, the European Association of Urology (EAU) guidelines also state that fluorescence-guided biopsy and resection are more sensitive than the more conventional procedure for the detection of malignant tumors, particularly CIS (evidence level 1a) [18].

Does Decrease in Tumor Recurrence Translates into a Decrease in Tumor Progression

Blue light cystoscopy was first implemented in clinical practice in the USA almost 10 years ago and has been used in Europe for nearly 20 years. As mentioned earlier in the article, the cumulative evidence indicates that improved tumor detection with blue light cystoscopy translates into reduced and more prolonged recurrence-free survival following TURBT. Particularly compelling are the results of a phase III, randomized controlled trial of 814 patients with suspected bladder cancer [12]. All patients underwent white light cystoscopy and TURBT with or without HAL-BLC before and after resection. A statistically significant reduction in recurrence at 9 months in favor of HAL-BLC (47 versus 56%; $P = 0.026$) was reported. It was also noted that the rate of recurrence of higher risk tumors, defined as CIS, T1 or ≥ T2, was reduced in the HAL-BLC group (16 versus 24%; $P = 0.17$). The study investigators later reported longer-term follow-up on 551 patients and noted that at a median of 54 months, 38% of patients in the blue light group remained tumor-free versus 31.8% in the white light group (median time to recurrence; 16.4 versus 9.6 months, respectively; $P = 0.04$) [14]. There was also a trend towards a reduced risk of developing MIBC as well as undergoing a radical cystectomy in the blue light group. Several additional prospective studies uniformly confirmed the reduced rates of tumor recurrence with the use of HAL-BLC, but the studies were not directly designed to assess impact on tumor progression rates [8, 19].

Disease progression may be the most concerning clinical event in an individual with NMIBC as progression is an independent predictor of disease-specific mortality [20–22]. The use of maintenance BCG for high-risk NMIBC reduces progression rates; however, the data for HAL-BLC favorably impacting progression are less clear [23, 24]. Historically, progression had been defined as developing MIBC; however, other reports have used different definitions of progression and it has become difficult to compare studies or even provide reliable patient counseling. Recently, the International Bladder Cancer Group (IBCG) initiated a proposal to consider a broader definition of tumor progression in NMIBC to coincide with clinical events that predict for poorer prognosis [25]. The proposal suggested defining progression as any one of the following: (1) the development of MIBC (T2–T4), progression to lymph node (N+) or distant (M1) metastasis; (2) an increase in clinical stage leading to invasion of the lamina propria (T1); (3) an increase in grade from low to high.

As noted earlier, in the pivotal phase III trial that led to HAL-BLC FDA approval, progression was defined as developing MIBC, and there was a non-significant trend toward lower risk of progression among patients who underwent HAL-BLC [12]. After a median follow-up of 4.5 years, eight patients in the blue light group and 16 patients in the white light group progressed to stage T2–T4 disease [14]. When the same study was re-analyzed using the broader definition of progression proposed by the IBCG, as expected, the number of progression events increased in both groups [26]. Specifically, 31 (12.2%) patients in the blue light group progressed compared with 46 (17.6%) patients in the white light group. The difference in rates of progression trended toward statistical significance, favoring the blue light group ($P = 0.085$), and blue light cystoscopy was associated with a trend toward improved progression-free survival ($P = 0.05$).

A recent systematic review and meta-analysis also concluded that the use of HAL-BLC reduced the likelihood of progression following TURBT [27•]. The study defined progression as developing MIBC and included four randomized studies and one retrospective study and analyzed 1301 patients. After a median follow-up of 38 months, progression was reported in 44 of 644 patients (6.8%) who received HAL-BLC and 70 of 657 patients (10.7%) who underwent white light cystoscopy alone (median odds ratio 1.64, 95% CI 1.10–2.45; $P = 0.01$). Therefore, the odds of progression were 64% higher among patients who did not have the additive benefit of blue light cystoscopy.

It is possible that blue light cystoscopy may reduce tumor progression rates in more than one way. Conceptually, this includes a better overall quality of TURBT by detecting unrecognized tumors and greater confidence that all visible diseases were removed but it is also possible that HAL-BLC improves tumor risk stratification that may lead to a change in treatment plan. A recent study analyzed data recorded from 641 HAL-BLC procedures (April 2014–December 2016) from a prospective multicenter registry that included nine institutions in the USA [29•]. The registry included patients with suspected or known NMIBC based on prior cystoscopy or imaging. In this "real-world" study, blue light cystoscopy increased detection of papillary tumors by 12% and increased detection of CIS tumors by 43% when compared with white light cystoscopy alone. As a result of the additional tumor(s) identified by blue light cystoscopy, there was a change in AUA risk group in 33 (6%) patients as well as a recommended change in treatment plan in 74 (14%) patients. Change in management was defined as initiation of intravesical therapy when it was not planned, increase in duration of intravesical therapy, or proceeding to radical cystectomy. Overall, 49 patients (9.3%) underwent radical cystectomy and urinary diversion. The indications for surgery included ≥ T2 disease (14 patients), recurrent multifocal HGT1 ± CIS (22 patients), and BCG unresponsive CIS (13 patients). Four of the radical cystectomies (8%) were performed exclusively because of findings detected by HAL-BLC alone [29]. A recent single-institution retrospective study suggests that even when analyzing patient survival rates after radical cystectomy, those who had at least one prior blue light TURBT for the management of NMIBC had better 5-year cancer-specific survival when compared with individuals who never had a blue light TURBT [31]. This study similarly supports the notion that HAL-BLC improves risk stratification and possibly more timely clinical decisions leading to improved oncologic outcomes.

In summary, while more research is needed, there is limited data suggesting that blue light cystoscopy can delay progression in NMIBC by earlier tumor detection, better quality TURBT, and improving disease risk stratification and subsequent treatment decisions.

Blue Light Flexible Cystoscopy in the Clinic (Surveillance)

In 2010, the Food and Drug Administration (FDA) approved HAL-assisted blue light cystoscopy for exclusive use in the operating room during TURBT of suspected NMIBC or the evaluation of positive urine cytology. As the body of evidence accumulated that earlier detection of tumors by blue light cystoscopy at the time of TURBT led to less cancer recurrences, there was growing interest in studying whether incorporating blue light cystoscopy in the office surveillance setting could further improve patient outcomes.

White light cystoscopy has been the standard of care for office bladder cancer surveillance for decades as it has a high sensitivity for detecting papillary tumors. However, a known limitation of white light cystoscopy is in detecting the presence of *carcinoma* in situ as it may be missed in as many as 20% of patients [32]. A prospective phase III clinical study was recently conducted that evaluated whether the addition of HAL-assisted blue light flexible cystoscopy (BLFC) to white light flexible cystoscopy (WLFC) for patients with intermediate or high-risk NMIBC during office surveillance led to improved cancer detection, including *carcinoma* in situ [33••]. The trial was an open-label, comparative, within-patient, controlled phase III study that included 17 centers in the USA. The study enrolled 304 patients, including 202 who had a prior history of high-risk NMIBC. Patients were excluded from the study if they had received any type of intravesical therapy in the 6 weeks prior to surveillance cystoscopy. All patients received intravesical instillation of HAL at least 1 hour prior to cystoscopy, and urine cytology was collected at the surveillance visit. Importantly, the results of the urine cytology were not known at the time of the surveillance visit and were not used in the decision of whether to proceed to TURBT.

All patients enrolled in the study underwent an initial evaluation with WLFC, and the characteristic, size, and location of all suspected malignant lesions were recorded. Following completion of WLFC patients was then randomized on the procedure table whether or not to proceed with BLFC. The same characterization was performed with BLFC and the information recorded. The rationale for the randomization was to help ensure that the study physician performed the initial WLFC diligently as it would not be known to the urologist whether BLFC would also be included in the care of the patient. At the conclusion of the cystoscopy, the trial mandated that a patient with any suspicious findings, by either white or blue light, needed to be further evaluated in the operating room, including HAL-BLC and TURBT. The primary efficacy end point of the trial was the proportion of patients with histologically confirmed malignancy that was detected only by BLFC and not by WLFC. The primary safety end point was the number of patients who experienced adverse events attributed to HAL or blue light cystoscopy.

Based exclusively on office cystoscopy, 103 patients in the study were taken to the operating room because of at least one finding suspicious for cancer, and 63 (61%) had histologically confirmed bladder cancer on central pathology review. All but one of the suspicious lesions confirmed histologically to be cancer were visible by BLFC, and importantly in 13 patients (21%), the cancer was only visible by BLFC and not WLFC. This included 5 patients diagnosed with *carcinoma* in situ who had a normal white light cystoscopy, and none of these patients was urine cytology positive or suspicious for cancer. This finding emphasizes the improved sensitivity of office-based enhanced cystoscopy in diagnosing *carcinoma* in situ when compared with both white light cystoscopy and urine cytology. In this study, the false-positive rate of suspicious lesions was 9.1% for both BLFC and WLFC.

Safety of Repeat Use of Hexaminolevulinate

Another important component of the phase III study evaluating blue light flexible cystoscopy was assessing the safety of repeated administration of HAL [33••]. Patients included in the trial were specifically questioned about adverse events after completing the surveillance cystoscopy as well as after TURBT. Each individual investigator determined whether the recorded adverse event was likely caused by HAL and whether the event was deemed serious.

Six patients experienced HAL-related adverse events following surveillance cystoscopy (2.0%) and three patients experience HAL-related adverse events following TURBT (2.9%). The adverse events included dysuria, bladder discomfort, erythema, and pruritus following surveillance as well as bladder pain and contact dermatitis following repeat use of HAL after the TURBT. Other than the 103 (33.8%) patients who received two doses of HAL during the study period, as per protocol, an additional 122 (40.1%) patients received at least two lifetime doses of HAL (i.e., prior HAL-BLC), including 90 (29.6%) patients who received three or more doses of HAL [33••]. Previous exposure to HAL did not affect the likelihood of adverse events compared with patients with no previous exposure to HAL. The clinical trial concluded that repeat use of HAL was safe and confirmed the conclusions of previous retrospective reports [35•, 37]. On the basis of these results, the FDA (2018) lifted the restriction on single use of HAL [38].

Future Directions

Photodynamic therapy is reliant on a photosensitizing agent that concentrates selectively in malignant cells. Following exposure to ultraviolet light, cells sequestering the photosensitizing agent can conceivably be destroyed by this methodology. The administration of HAL intravesically leads to preferential accumulation of protoporphyrin IX in the mitochondria of urothelial cancer cells. The excess accumulation of protoporphyrin IX, a photoactive compound, can be excited by specific wavelengths of light and suggests conceptually that this may be a means of destroying urothelial cancer cells [39].

A prospective study of 17 patients with a marker lesion studied the therapeutic efficacy of HAL at concentrations of 8 mM and 16 mM accompanied by bladder wall irradiation from an incoherent white light source that emitted light in the visible spectrum from 380 to 700 nm [40]. The first 14 patients received three treatments with a light dose of 100 J/cm^2 every 6 weeks, and the remaining three patients were treated at increasing intensities of light dose from 25 to100 J/cm^2 on the same schedule as the other patients in the study. The results of the study were interesting as 9 patients (52.9%) were tumor-free at 6 months and 4 patients (23.5%) were tumor-free at 9 months, and 2 (11.8%) remained without tumor at 21 months [40].

Well-designed clinical trials to test HAL as a photodynamic therapy are warranted as this may obviate the need for or complement currently used adjuvant intravesical therapies.

Conclusions

Individuals diagnosed with NMIBC are prone to tumor recurrence and some are even at high risk of disease progression. A considerable body of evidence supports that integrating HAL-BLC at the time of TURBT for suspected NMIBC reduces subsequent cancer recurrence rates. It is surmised that this benefit is achieved by better visualization of previously unidentified tumors, better overall quality of TURBT, and possibly more accurate risk stratification leading to changes in clinical management. Ultimately, progression of NMIBC may be the most important clinical event as it is associated with increased cancer-specific mortality. The current evidence, albeit preliminary and in need of better-designed studies, suggests that TURBT performed with HAL-BLC is also associated with a lower risk of later developing MIBC and other progression events. The strength of the evidence of HAL-BLC favorably impacting bladder cancer outcomes has led to its inclusion in the American and European bladder cancer guidelines.

Another opportunity to impact outcomes favorably in NMIBC is using enhanced cystoscopy in the office surveillance setting. A recently completed trial confirmed that HAL-assisted flexible blue light cystoscopy increased the detection of cancerous lesions over white light cystoscopy, including high-grade lesions. The trial also confirmed that repeated doses of HAL are safe and can be used in the continuum of care in a patient diagnosed with NMIBC. Further evidence

will be needed to confirm that the earlier detection of cancerous lesions at the time of surveillance cystoscopy leads to a clinically meaningful impact in patient care.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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