Photodynamic diagnosis for follow-up of carcinoma in situ of the bladder

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Introduction: A prospective study to evaluate the reliability of cystoscopy was performed with fluorescence (photodynamic diagnosis, PDD) compared with standard white light (WL) cystoscopy in patients with solitary carcinoma in situ (CIS), undergoing BCG treatment.

Materials and methods: Between February 2004 and March 2006, 49 patients suffering from CIS were enrolled in the study. Patients age was 68.5 ± 13.5 years (mean ± SD) and all presented CIS alone at inclusion. All suspicious areas were biopsied either under white light or blue light. Urine cytology was peformed on each patient before endoscopy.

Results: Out of 49 patients enrolled, 15 (30.6%) presented with positive urinary cytology. Out of 18 patients positive to CIS at biopsy, 14 (77.7%) could be diagnosed exclusively by means of PDD cystoscopy and transurethral bladder resection and 4 (22.3%) during both standard and PDD cystoscopy. No additional CIS could be diagnosed by standard WL cystoscopy alone. The overall false positive rate for PDD accounted for 33.3% compared with 7.1% for WL cytoscopy. A statistical correlation was documented between the number of CIS findings and PDD ($r = 0.6976$, $p = 0.0002$) while WL cystoscopy ($r = 0.1870$, $p = 0.3816$) and urinary cytology ($r = 0.4965$, $p = 0.0136$) correlated only weakly with CIS. The overall side effects related to the drugs were negligible overall.

Conclusions: These data show that PDD cystoscopy is more reliable than WL cytoscopy for the follow-up of CIS patients during BCG treatment. Long-term data and multicenter, prospective data are needed to assess the true impact on tumor recurrence and progression.

Keywords: bladder cancer, fluorescence, carcinoma in situ, endoscopy

Introduction

Carcinoma in situ (CIS) of the bladder still represents one of the most challenging issues in urological oncology. Urinary cytology and conventional cystoscopy with bladder mapping have represented the golden standard diagnostic tools for many years (Witjes 2004). In spite of their overall high sensitivity and specificity, the incidence and prevalence of CIS have continued to be underestimated (Lamm 1992). Urinary cytology cannot provide information regarding the location and the extent of this tumor, and suffers from the limitations related to the subjective skill of the referral pathologist (Raitanen et al 2002). On the other hand, there is a general agreement that a delay in the recognition of this disease, mainly when resistant or recurrent after intravesical immunotherapy, can be responsible for tumor progression, as documented by the consistent amount of patients with positive lymph nodes at the time of radical cystectomy. To date, none of the new markers has proved to be superior to standard urinary cytology in improving our ability to detect and treat CIS (Sylvester et al 2005). Since the first experience published in the 1990s, porphyrin-induced fluorescence associated with cystoscopy (photodynamic diagnosis, PDD) or transurethral bladder resection (TUR), has progressively gained a relevant position among the diagnostic procedures and the endoscopic treatments of superficial bladder cancer (Kriegmair et al 1995). Recent studies have provided indubitable evidence that PDD can actually

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play a key role in the diagnosis of flat lesions, either single tumor presentation or concurrent with papillary tumors (Zaak et al 2005). The very high sensitivity and the excellent safety profile certainly represent the most relevant advantages of this approach. The non-negligible rate of false positive results, the uncertain reliability when performed during the follow-up of patients undergoing intravesical therapy, and the global cost are generally considered as the most consistent limitations of this procedure. Although several porphyrin-derived drugs are under investigation for PDD, only two are currently used: 5-aminolevulinic acid (5-ALA), the first to be introduced, and its more potent ester hexaminolevulinate (HAL) (Zaak et al 2005).

In this study we sought to compare the blue light cystoscopy (PDD) with the standard white light (WL) cytoscopy, in a particular subgroup of patients suffering from CIS alone at inclusion and undergoing therapy with endovesical immunotherapy (Bacillus Calmette-Guérin, BCG).

Methods

Between February 2004 and March 2006, 49 patients suffering from CIS alone at the time of study inclusion undergoing BCG treatment (OncoTICE®, 50 mg, BCG TICE strain, 1 to 8 x 108 colony forming units per instillation dose) according to the SWOG (South Western Oncology Group) maintenance schedule, were enrolled in this prospective study. Primary endpoint of the study was to compare the reliability of PDD-guided bladder mapping with WL cytoscopy and urinary cytology for the followup of CIS patients under BCG treatment. All PDD procedures were carried out by the same surgeons (RC, RN).

The PDD-system components used were Richard Wolf (Germany) and Storz (GmbH, Tuttlingen, Germany) dedicated instruments. For both systems, the light source used to produce fluorescence excitation was a filtered white light fitted with a xenon lamp (300 W) delivering a wavelength between 380 and 440 nm. All the examinations were performed using specific PDD telescopes (0°, 12°, 25°, and 70° according to the tumor location) and software for video-image reconstruction. All procedures were performed suing intravesical fluorescence-inducing drugs such as 5-aminolevulinic acid (5-ALA hydrochloride 1.5 mg dissolved in 50 mL of 3.5% sodium monohydrogenophosphate solution; Medac GmbH, Wedel Germany-Shering) in 20 cases (40.9%) and HAL 85 mg (HAL hydrochloride; Hexvix®, Photocure™, GE Healthcare) in the other 29 (59.1%). After adequate time of bladder instillation, bladders were totally voided from any residual solution prior to starting the endoscopic procedure. A standard WL cystoscopy was always performed as a first step of the evaluation and all suspicious areas were accurately described and reported on a bladder map. Thereafter, a fluorescence cystoscopy was accurately performed and any suspicious area was reported on the same map. In addition, any side effect related to the drugs was described. Cold cup biopsies and/or deep biopsies were taken by standard resection and biopsies were collected from any suspicious area either under blue or white light. Whenever no suspicious areas could be seen, a standard random mapping including 8 biopsies overall was completed.

Patients were recruited for the study at any moment of the SWOG maintenance schedule. Three weeks were defined as the minimum time between last bladder instillation and endoscopic evaluation. Table 1 shows patient characteristics including pre-study bladder cancer and history. All patients necessarily provided urinary cytology on three voided samples at time of the endoscopy. While cytological evaluation was performed by different pathologists, all histological evaluations were systematically examined by the same uropathologist blind to the study, according to the 1973 WHO diagnostic criteria. All patients signed an informed consent prior undergoing the procedure. Side effects were assessed directly by the hospital staff directly during hospitalization. The patients were seen on outpatient basis and verbally assessed for any post-operative complication.

Data were analyzed using commercially available statistical software and are presented as mean ± SD. For all statistical comparisons, significance was defined as a p value of less than 0.05.

Results

The mean time of the bladder instillation was 160 min (range: 100–180) and 85 min (range: 30–120) for 5-ALA and HAL respectively. In particular, only 3 patients who received HAL kept the drug for less than 60 min due to reduced bladder capacity.

Table 1 Patient characteristics (mean ± SD)

Number of patients	49
Mean age (years)	70 ± 12
Time from last bladder instillation (days)	68 ± 28
Number of bladder instillations/patient (BCG)	16 ± 10
Bladder cancer history	
TaG1 + CIS	3
TaG2 + CIS	5
T1G2 + CIS	2
T1G3 + CIS	12
Previous CIS alone	27

Abbreviations: BCG, Bacillus Calmette-Guerin; CIS, carcinoma in situ.

Table 2 Carcinoma in situ detection

Positive urinary cytology	15 (30.6%)
Total CIS diagnosed	18 (36.7%)
CIS diagnosed with PDD + Standard WL cystoscopy	4 (8.2%)
CIS diagnosed only with PDD	14 (28.5%)
CIS diagnosed with WL only	0
Overall PDD false positives	9 (33.3%)
Overall WL false positives	1 (7.1%)

Abbreviations: CIS, carcinoma in situ; PDD, photodynamic diagnosis; WL, white light.

Out of 49 patients enrolled, 15 (30.6%) presented with positive cytology at the time of investigation and overall 18 (36.7%) resulted positive for CIS at bladder mapping. Among those, 14 (77.7%) were diagnosed exclusively by means of biopsies guided by PDD while 4 (22.2%) were diagnosed during both the standard and PDD cystoscopy. On the other hand, no additional CIS was diagnosed with standard cystoscopy only. In 9 cases of suspicious areas at fluorescence cystoscopy, 7 cases were diagnosed as inflammatory tissue and 2 as mild dysplasia. As a consequence, the overall false positive rate accounted for 33.3%. In particular there were 5 PDD false positives in the 5-ALA group (35%) but in the HAL group there were 4 (22.7%, $p < 0.005$).

An overall statistical correlation could be found between the number of CIS documented by histology and fluorescence ($r = 0.6976$, $p = 0.0002$) while white light ($r = 0.1870$, $p = 0.3816$) correlated only weakly with CIS detected and urinary cytology seemed to correlate with CIS ($r = 0.4965$, $p = 0.0136$). Furthermore, no correlation was observed between cytology and white light ($r = 0.0374$, $p = 0.8623$).

In two patients with positive cytology, no suspicious area within the bladder could be observed by both standard and PDD cystoscopy. According to the design of the study, these patients underwent random bladder mapping which definitively resulted negative for bladder cancer. A subsequent separate ureteral selective cytology was documented to be positive in both patients, suggesting proof of upper urinary tract CIS. No systemic side effects related to the procedure were reported while local side effects were referred as negligible from all patients.

Discussion

However easily defined, the ideal diagnostic tool for bladder cancer detection and monitoring is still far from being found. The ideal test should be simple to perform, affordable and should provide the highest levels of sensibility and specificity. The association between urinary cytology and standard WL cystoscopy are still considered as the elective diagnostic approach for CIS of the bladder (Sylvester et al 2005). However, the sensitivity and specificity of urinary cytology vary throughout the literature due to its well known limitations, such as limited amount of retrieved cells, inter- and intra-observer variability, and alterations related to inadequate preservation of the voided specimens. In addition, as well known, pathologist interpretation can become misleading in cases of concomitant urinary infections and during intravesical chemo- or immuno-prophylaxis (Raitanen et al 2002). Moreover, evidence can be found in the literature attesting that standard bladder mapping with random biospies taken under white light has little value from both diagnostic and prognostic points of view (Kiemeney et al 1994; Sylvester et al 2005). Recent published guidelines (Sylvester et al 2005) have highlighted the increasing role of photodynamic endoscopy especially for the diagnosis of bladder CIS and dysplasia. On the other hand, PDD-guided TUR of papillary tumors seems to significantly reduce residual tumor, providing a positive impact on the reduction of the recurrence rate (Zaak et al 2005). The feasibility and superiority of PDD using 5-ALA compared with WL cystoscopy for the diagnosis and follow-up of flat lesions such as CIS and moderate dysplasia has already been well documented (Riedl et al 2001; Zaak et al 2001, 2002; Filbeck et al 2002; Daniltchenko et al 2005)

Most of the studies conducted up to now have helped to establish the reliability of PDD performed by means of 5-ALA as first choice drug (Zaak et al 2005). However, some more recent investigations have documented the superiority of HAL over 5-ALA due to both enhanced fluorescence and need for shorter drug instillation time (Filbeck et al 2003; Schmidbauer et al 2004; Jochamn et al 2005; Loidl et al 2005; Witjes et al 2005). When using HAL, Schidbauer et al (2004) showed that among 83 patients with CIS, the diagnosis could be obtained by HAL cystoscopy only in 18 (22%), by both standard and HAL cystoscopy in 62 (75%), and by standard cystoscopy only in 2 (2%). According to this experience, PDD cystoscopy was able to detect 28% more patients with CIS compared with WL cystoscopy.

In a multicenter study using HAL and involving 146 patients, Jocham et al (2005) described an important improvement using PDD, accounting for an additional detection in 38 cases (24.4%). Based on this result, the authors could usefully influence both intra- and post-operative management in a consistent number (17%) of their cases. In spite of this evidence, at present only a few centers in Europe are equipped for the PDD procedure and even

fewer routinely perform PDD. We can assume that the most important limiting factors are: cost for the start-up treatment (dedicated equipment); cost and availability of fluorescent drugs; necessity to plan the procedure in advance; and the need for some training in its. In order to answer the question concerning the cost/benefit balance of this procedure, the definition of a widely accepted algorithm which defines when PDD should be recommended becomes of pivotal importance. Currently, the most evident clinical impact of PDD has been demonstrated for a) the management of any form of CIS, b) T1G3 patients in follow-up after TUR, c) multifocal disease during TUR or follow-up.

From the beginning of our practice, we decided to systematically perform PDD investigation for patients suffering from CIS alone in follow-up during BCG maintenance treatment. At evaluation time, out of an overall 49 patients, 15 presented with positive cytology while 18 were diagnosed with CIS at biopsies. Out of all the patients diagnosed with CIS, 14 were detected by means of PDD only and 4 by PDD + WL cystoscopy, a surprisingly higher additional detection rate in favor of PDD. On this basis, the detection rate of WL cystoscopy was consistently lower than that usually reported in the literature (Sylvester et al 2005), suggesting again its controversial role for the management of patients undergoing BCG treatment. A possible reason for these results could be related to the relatively low number of patients enrolled per arm. When compared with the number of positive cytology cases, PDD-guided biopsies achieved an additional detection rate of 20%. Furthermore, according to our experience, when a positive cytology exists alongside negative biopsies at PDD, a CIS of the upper urinary tract should be suspected .

On the other hand, due to the higher PDD sensitivity documented in this study and in accordance with Kriegmair et al (2002), one can assume that, in cases of complete negative cystoscopy both in white and blue light, bladder mapping can be safely avoided.

In addition, the higher reliability of PDD compared with standard WL cystoscopy for the diagnosis of CIS in patients under BCG treatment appears to be evident regardless of the overall number of instillations performed during the SWOG schedule of administration. Photodynamic diagnosis performed using HAL together with biopsies taken by TUR seemed to achieve a higher CIS detection-rate than that obtained using 5-ALA and cold cup biopsies. On the other hand, a consistent overall rate of false positives (32.1%) was registered for PDD regardless of the method used. However, multicenter, randomized studies comparing the two drugs are needed to accurately assess any differences in detection rate. In order to reduce the incidence of false positive findings, Grimbergen et al (2003) proposed a cut off period of 6 months after the last instillation as the suitable time for performing a reliable PDD cystoscopy. However, the key question is whether the benefit of an early detection and an adequate management of a potential aggressive disease such as CIS could be preferable to the risk of performing useless biopsies.

Based on this experience we can assume that: the detection rate of PDD cystoscopy is higher than that provided by urinary cytology; WL cystoscopy alone is not reliable for the follow-up of CIS under BCG treatment; the overall side effects of PDD are negligible; PDD with HAL associated with TUR seems to be superior to PDD with 5-ALA associated with cold cup biopsies. However, there is no doubt that this study suffers from many limitations, pitfalls, and potential biases related to the different variables presented. We are certainly aware that these results should be considered only as preliminary and need to be confirmed by studies with a large series of patients.

Conclusions

The high recurrence rate of non-muscle invasive bladder cancer, up to 70% at 5 years, is clearly responsible for the high prevalence and social cost of this disease and represents a huge workload for urologists as well as a dramatic inconvenience for patients. There is no doubt that novel diagnostic and therapeutic approaches are urgently needed.

During the last decade, the role of PDD has progressively increased for both treatment and the surveillance of patients with transitional cell carcinoma of the bladder. Many studies have clearly proved that PDD-guided cystoscopy using 5-ALA can significantly improve the overall detection rate of tumors, especially when flat otherwise invisible lesions are in question. CIS is notoriously difficult to recognize during standard WL cystoscopy, as it can generally appear macroscopically identical to normal urothelium. However, it is also well known that the progression rate of untreated CIS to invasive disease is about 50% and missed cases may be responsible for progression in otherwise low-risk patients. As well as CIS, there have been reports that PDD can be used to detect bladder dysplasia with much greater sensitivity than WL cytoscopy. The significance of this outcome remains uncertain; however, since evidence suggests that dysplasia is frequently associated with progression of non-muscle invasive tumor disease, it will be of interest to investigate whether the increased detection of severe dysplasia could allow for a better definition of this controversial issue.

A recognized limitation of PDD cystoscopy is represented by the increased rate of false positive results when compared with standard WL cytoscopy. This limitation becomes crucial in conditions such as acute and chronic inflammation of bladder mucosa and when intravesical chemo-or immunoprophylaxis of recurrence after transurethral resection is ongoing.

Previous experience showed that patients who had undergone recent intravesical chemotherapy (within 6 months) had significantly more false-positive biopsies at PDD cystoscopy than those for whom more than 6 months had elapsed since local therapy or who had never had it.

Our study, which was designed especially to investigate the actual role of PDD for the detection of failures in an homogeneous series of patients suffering from CIS during maintenance intravesical BCG treatment, seems to demonstrate that PDD can significantly increase the detection rate of CIS also in this special cohort of high risk patients.

In addition, our study confirmed that PDD is a safe and relatively easy procedure to learn.

However, in spite of all the mentioned advantages, at present the PDD technique is not in widespread use. As a limiting factor, apart from the cost for PDD equipment and limited availability of the fluorescent drugs, the fact that clinicians are still unsure of exactly which patient subgroups are best candidates for this technique probably plays a crucial role. Moreover, an accurate cost/effectiveness analysis of this procedure is still lacking in the literature (Colombo 2007).

Prospective and multicenter studies with long-term follow up are needed in order to determine the global impact of the improved tumor detection rate using PDD on recurrence, progression, and survival.

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