Long-term outcome of intravesical bacillus Calmette–Guérin therapy with maintenance for urinary bladder carcinoma in situ: About 47 cases

Evolution à long terme du carcinoma in situ de la vessie traité par BCG thérapie endo-vésicale: A propos de 47 cas

Sataa Sallami[1], Hassen Khouni[2], Mahmoud Ben Atta[3], Sana Abou El Makarim[1], Mohamed Bechir Zouari[4], Sami Ben Rhouma[5]

1-Service d'urologie-CHU Mohamed Tahar Maamouri - Nabeul - Tunisie / Faculté de médecine de Tunis
2-Service d'urologie-CHU forces de sécurité interne - La Marsa -Tunisie / Faculté de médecine Sousse
3-Service de chirurgie urologique - EHU Oran - Algérie
4-Faculté de médecine de Tunis
5- Service d'urologie-CHU la Rabta / Faculté de médecine de Tunis,

RÉSUMÉ

Introduction: Les données relatives à l'efficacité du Bacillus de Calmette-Guérin (BCG) en instillations intravésicales sur le carcinome in situ (CIS) de la vessie sont limitées.

Objectifs: Analyser les résultats à long terme du traitement du CIS de la vessie par BCG endovésicale, évaluer son efficacité et innocuité et determiner les facteurs pronostiques qui pourraient prédire la récidive et la progression de la maladie.

Méthodes: Entre Mars 1994 et Décembre 2010, 47 patients (hommes:40; femmes: 7) âgés de 40 à 71 ans (médian d'âge de 59,5 ans) et porteurs d'un CIS de la vessie, ont était traité par instillation hebdomadaire endovésicale de BCG (75 mg de souche Pasteur) pendant six semaines suivie par 6 instillations mensuelles. Les patients ont été recueillis auprès de quatre différentes institutions.Le diagnostic a été fait sur des biopsies randomisées de la muqueuse vésicale (n = 19), une lésion macroscopique (n = 28) et la cytologie urinaire (n = 6).Un CIS primaire (Groupe I), concomitant (Groupe II), et secondaire (Groupe III) a été trouvé dans 13 (27,6%), 28 (59,6%) et 6 (12,7%), des patients, respectivement.

Résultats: La période de suivi médiane était de 67,5 mois (60-116 mois).Les taux de récidive étaient de 15,4%, 35,7% et 50% respectivement dans le groupe I, II et III à 5 ans de suivi. Le taux global de réponse complète était de 68%.Le taux de survie sans progression à 5 ans était de 87,2%.Plusieurs facteurs, comme l'âge (<60 ou> 60 ans), le genre, les antécédents de résection endoscopique et le type du CIS ont été examinés par une analyse multivariée pour prédire la progression. Aucun d'entre eux n'était un facteur pronostique indépendant.Les symptômes d'irritation vésicale étaient les principaux effets indésirables de la BCG thérapie. Il n'y avait pas d'effets indésirables graves nécessitant l'arrêt du traitement.Une cystectomie radicale a été réalisée chez 5 patients. L'extension extravésicale a été identifiée chez un seul patient. Pendant la période de suivi, aucun patient n'est décédé par cancer de la vessie.

Conclusion: Le traitement du CIS vésical par BCG thérapie est particulièrement efficace et inodin pour le CIS primaire et concomittent, pouvant être des facteurs pronostiques. On n'a pas trouvé de facteur de risque significatif. La récidive et la progression, y compris l'extension extra-vésicale doiventt être attentivement surveillé à long terme après BCG thérapie.

Mots-clés

Cancer de la vessie, Carcinoma in situ, Bacille Calmette-Guérin, souche Pasteur, Instillation, Effet secondaire, Cytologie, Cystoscopie, Récidive, Progression, Pronostic.

SUMMARY

Introduction: Data concerning the efficacy of intravesical Bacillus Calmette-Guerin (BCG) on carcinoma in situ (CIS) of the bladder are limited.

Objectives: We analyzed long-term outcomes of instillation therapy with BCG to treat bladder CIS, evaluated its effectiveness and safety and searched for prognostic factors that could predict disease recurrence and progression.

Methods: Between March 1994 and December 2010, 47 patients (male: 40; female: 7) with median age of 59,5 years (range 40-76 years), diagnosed with bladder CIS underwent weekly BCG instillations (75 mg of Pasteur strain) for six weeks followed by 6 monthly instillations. Patients were collected from four different institututions.Proven bladder CIS diagnosis was made through random biopsy (n=19), macroscopic lesion (n=28) and urinary cytology (n=6). Primary, concomitant, and secondary CIS was found in 13 (27,6%), 28 (59,6%) and 6 (12,7%), patients, respectively.

Results: The median follow up period was 67.5 months (range 60-116 months).The rcurence rates were 15,4%, 35,7% and 50% respectively in group I,II and III at 5 years follow-up. The overall complete response rate was 68%. The five-year progression-free survival rate was 87.2%.

Several factors, such as age (<60 or >60 years), gender, previous transurethral resection and type of CIS, were examined by multivariate analysis to predict recurrence and progression. None of them was an independent prognostic factor.

Bladder irritation symptoms were the main BCG adverse effects. There were no severe adverse effects requiring discontinuation of drug administration.Radical cystectomy was performed in 5 patients. Extravesical involvement was identified in only one patient. During follow-up period, none died of bladder cancer.

Conclusion: Therapy with BCG is remarkably effective and safe for primary CIS and concomittent CIS, which might be a prognostic factor. We didn't find any significant risk factor. Recurrence and disease progression including extravesical involvement should be carefully monitored over the long-term after BCG therapy.

Key-words

Bladder Cance, Carcinoma in situ, Bacillus Calmette-Guerin, Pasteur strain, instillation, adverse effect, Cytology, Recurrence, Progression Cystoscopy, Prognosis

Carcinoma in situ (CIS) of the bladder is a flat, high-grade, intraepithelial malignancy of the urothelium (1). Although non-invasive, this enigmatic condition is usually considered as a malignancy owing to its high risk of progression to invasive bladder cancer (2,3).
The aggressive natural history of CIS of the bladder has been well established (4,5). Without treatment, patients progress to locally invasive disease and subsequently to metastatic disease (4,5). Approximately 60% of patients with CIS managed by transurethral resection (TUR) alone have progression to muscle invasion, and a third die of bladder cancer within 5 years (4,5-7).
CIS may present de novo or as recurrence after treatment of nonmuscle invasive bladder cancer (NMIBC), and is frequently associated with high grade NMIBC (3).
Intravesical bacillus Calmette–Guérin (BCG) therapy is actually the standard treatment for CIS (2,5,6). However, some patients still show no response or frequently recur after initially responding to the treatment.

OBJECTIVES

The aim of the present study is to report outcome and determin prognostic factors which can predict disease recurrence / progression in patients with bladder CIS treated with BCG instillations (standard course of 6 BCG instillations with maintenance treatment).

METHODS

A total of 50 patients with CIS who were treated with BCG were identified at the Rabta University Hospital, Mohamed Tahar Maamouri University Hospital, Internal Security Forces Hospital and Oran University Hospital. Three patients had no follow-up and thus were excluded from this report, leaving a total of 47.
We've included in this study, all patients with proven bladder CIS, who were followed-up for 5 year or more. Patients with history of NMIBC were also included.
Patients with history of muscle invasive transitional cell carcinoma, previous intravesical chemotherapy instillation, with active tuberculosis or on anti-tuberculosis drugs and those who failed to complete a full course of BCG instillations, were not included.
The clinical records were studied in all cases but no histopathological review was performed.
Bladder CIS was diagnosed from random cold-cup mucosal biopsies (five bladder sites: trigone, posterior wall, left side wall, right side wall, dome, and prostatic urethra), by endoscopic resction of suspicious lesions or by urinary cytology. Associated papillary tumors or other visible lesions were completely resected and a deep biopsy containing detrusor muscle was shown to be tumor-free. No early adjuvant intravesical chemotherapy was given. Bladder tumors were staged according to the 2009 TNM classification and graded using the WHO system (8). CIS tumor was classified into primary (group I), concomitant (group II), and secondary CIS (group III)(9) as follows; primary CIS means a CIS lesion was found without visible tumor with no history of bladder tumor, concomitant CIS means a CIS lesion was identified with visible tumor with no history of bladder tumor, secondary CIS means a CIS lesion was found during follow up of bladder tumor with or without visible tumor.
Treatment comprised 6 weekly induction instillations of 75 mg of Pasteur strain BCG in 50 ml of normal saline, starting 2 to 3 weeks after diagnostic biopsies and TUR of visible tumors.
One month after the final instillation, cystoscopy with at leat 6 random cold-cup mucosal biopsies and/or urine cytological examination were performed to evaluate clinical response. Bladder washings were collected at each cystoscopy, and TUR or pinch biopsies were performed if indicated. After verifying "tumor-free" at the first control, patients receive 6 monthly maintenance instillations (75 mg Pasteur strain BCG). Then, patients were followed in a routine schedule with cystoscopy and urine cytology every 4 months in the first 2 years, and every 6 months thereafter. A complete response (CR) was defined as negative urine cytological and random biopsy findings. An incomplete response (NR) was defined as biopsy proven bladder tumor or the presence of malignant cells in urine cytology.
Patients who did not achieve CR from the first cycle of BCG therapy underwent an additional 6 week cycle under the same conditions as stated above.
Recurrence was defined as positive cytology or a tumour that was resected or fulgurated. Progression was defined as detrusor muscle invasion, prostatic stromal invasion or metastatic disease (10). The initial end point selected for analysis was the complete response rate. Secondary end points at 5-year followup were recurrence- free survival, progression- free survival and cancer specific survival. The follow-up was censored at the date of the last control visit showing no evidence of disease.
The times to recurrence and progression were measured from the date of the first BCG instillation to the date of the first positive control diagnosing recurrence or progression.
The following variables were analysed: age, gender, risk factor for bladder cancer, previous stage T1 tumour, previous T1G3 tumour, previous intravesical BCG therapy, which group CIS belongs to, number of instillations, bothersome side-effects, results of the first control (3-months cystoscopy). In case of lack of data, the patient was convoquated and histological specimen considered again if necessary.

Statistic tests:
The recurrence-free, progression-free, and cancer specific survival rates were calculated by the Kaplan–Meier method, and statistically analyzed by the log-rank

method. Differences between groups were analyzed by χ^2 test, eventually completed by Fisher exact test and Student T-test. All tests were two-tailed and conducted at the 5% significance level. Relative risk and 95% confidence intervals were determined using SPSS (version 19.0) software (SPSS, Chicago, Illinois).

RESULTS

Between March 1994 and December 2010, 47 patients diagnosed with bladder CIS underwent BCG instillation at the four different hospitals.

They were 40 males and 7 females with a mean age of 59,5 years (range 40-71 years).

Medical history revealed endoscopic resection of prostate, removal of bladder stones, ureteral stenosis and endoscopic resction of NMIBC in 5, 2, 5 and 6 patients respectively. A history of stage Ta and the T1 NMIBC more than 1 year prior to inclusion were reported in three patients in each. From them, four had undergone endovesical BCG instillations.No patient had undergone previous intravesical chemotherapy. Twenty six patients (55,3%) were heavy smokers (> 30 pach years) and four patients had occupational exposure. Cystoscopy revealed bladder tumor in 27 patients ((57,4%), mucosal inflammation (n=5) and no visible tumor at all in the remaining 15 patients. Patients with visible tumors were treated by transurethral resection (TUR) of all visible lesions. These tumors were multiple in 22 patients.The diagnosis was made by urinary cytology (n=6), cold cup random biopsy (n=19) or TUR of the bladder mucosa (n=28). According to endoscopic data, CIS was in the left side wall (n=26), right side wall (n=9), dome (n=14), right meatus (n=5), left meatus (n=5), trigone (n=13), prostatic uretra (n=4) and posterior wall (n=12).

Thirteen patients presented with primary CIS, seven with CIS and low-grade Ta bladder tumours, twenty one with CIS and high-grade T1 bladder tumours and secondary CIS in six cases (Table I).

Table 1 : Comparaison of the 3 groups pf CIS primary CIS versus concomitant versus secondary

CIS group	Primary	Concomitant	Secondary	p
Nb	13	28	6	-
Age	58.4±3.1	61.3±2.2	57 ±3,7	0.83
Genre: M/F	10/3	25/3	5/1	0.58
Heavy smokers	5	17	4	0.34
CR after one cure	11	18	3	0.25
Recurrence (5 ys)	2	10	3	0.25
Progression (5 ys)	0	4	2	0.12

CR: complete response

All patients received a BCG induction course comprising 6 weekly instillations before the first follow-up cystoscopy / urinary cytology. Maintenance therapy was not performed in 5 patients only. The median follow up period was 67.5 months (range 60-116 months).

Clinical response:

The CR after one cure was 87,2%. Bladder CIS was found (at the first control) in 3 patients and in the second in 3 others. They underwent a second course of BCG instillation, which resulted in a complete response in three of them. Three patients have had recurrence of bladder tumor. The overall complete response rate was 68,0 % (n=32) and there was no significant difference between the three groups (p=0,25). Of the 13 patients with primary CIS, 11 (84,6%) showed CR after 1 cure, and 2 after 2 cures of BCG therapy. Of the 28 patients with concomitant NMIBC, 18 (64,2%) showed CR after 1 cure, and four after two cures of BCG therapy. Of the 6 patients with secondary CIS, three showed CR after 1 cure (Table II).

Table 2 : Comparaison between overall CR and recurrence patients

Parameter	CR (n=32)	Recurrence (n=15)	p
Age	60.6±5.4	57.8±1.7	0.87
Gender: M/F	27/5	13/2	0.83
History of bladder tumor	3	3	0.31
Tobacco > 30	15	9	0.40
Clinical signs:			
Hematuria	23	12	0.55
LUTS	21	9	0.71
Patient's CIS group:			
Primary CIS	11	2	1
Concomitant CIS	18	10	
Secondary CIS	3	3	

The seven patients, with NMIBC recurrence, were treated by iterative TURBT followed by BCG therapy.

The three patients with persistant CIS underwent other cycles of BCG instillation and showed CR in one case, but two of them subsequently had repeated recurrence without progression and finally were programmed for total cystectomy. Nine patients with a positive first control were tumour-free in the next cystoscopies.

Recurrence-free survival:

At the next controls, 15 patients developed recurrences with a median of 16,0 months (3-36).

Figure 1 shows that the five-year recurrence-free survival was 68%. Taken together, there was no significant difference between the three groups of patients (p = 0.24).

Progression-free survival:

The 5-year progression-free survival (PFS) rate was 87,2%. We found that PFS did not differ according to the type of CIS (p = 0.10) (Figure 2).

Sex patients progressed (between 3 and 30 months ith a median of 18,3 months to stage (pT2). Five patients underwent cystectomy (Bricker in 4 cases and enterocystoplasty in one case) and the last patient

refused surgery. He underwent chemotherapy with iterative endoscopic resection (follow-up 59 months).
Extravesical involvement was identified in the upper urinary tract in only one patient at 60 months of follow-up. He underwent radical uretero-nephrectomy. One patient developed local recurrence (12 months) and another one developed pulmonary metastasis after 17 months.

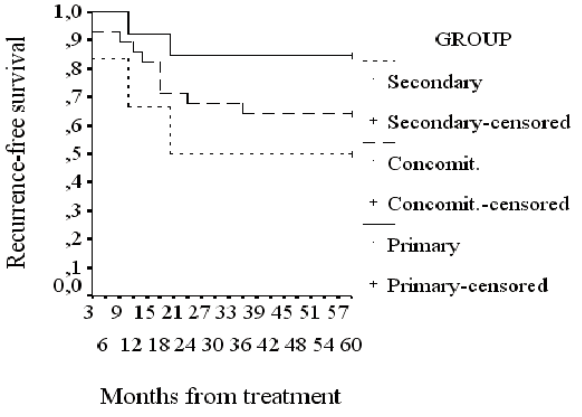

Figure 1: Kaplan–Meier curve of recurrence-free rate in primary, concomitant and secondary CIS respectively during follow-up for 5 years.

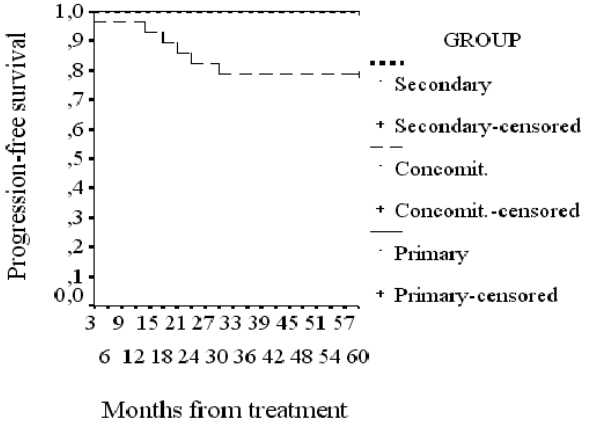

Figure 2: Kaplan–Meier curve of progression-free rate in primary, concomitant and secondary CIS respectively during follow-up for 5 years.

Mortality:
In this series, although none of the 47 patients died of bladder cancer, two died of unrelated causes. Therefore, 42 patients are currently alive with no evidence of bladder cancer and 3 were lost to follow-up.
Bothersome side-effects developed in 24 patients (51%), however treatment was not stopped. They were mainly urinary urgency (n=17), pain on urination (n=8) and pyuria (n=3). Gross hematuria and fever were not reported.
There were neither severe adverse effects requiring discontinuation of drug administration nor complications requiring medication with antituberculosis drugs or surgery.
The planned BCG treatment course was completed in all cases. Lowering the original dose to a half or a quarter in order to reduce toxicity was not required in any patient.
Parameter that may influence response to BCG therapy:
Statistical studies didn't reveal correlation between response to BCG therapy and the following parameters: age, gender, tobacco, clinical signs and group of CIS (Table II).
At 60 months folow-up, patients with or without concomitant NMIBC have the same evolution (Figure 1)

DISCUSSION

CIS accounts for 1-4% of the primary tumors and occurs concomitantly with a papillary tumor in 13-20% of the bladder cancer patients (11,12). This rate was 12,7% in the present series. Although CIS is included within the category of NMIBC or 'superficial' disease, this lesion has been recognised for its invasive potential aggressiveness and unpredictable nature. In two large Scandinavian series (11,12) with a total of 790 patients, more than half tumors with concomitant CIS were muscle-invasive at diagnosis and only 5% were NMIBC with concomitant CIS. Because of the low incidence, most series are small and therefore frequently analyzed together with other forms of NMIBC.
Urothelial CIS are easily missed at cystoscopy, but often better detected on cytology. Thus, the diagnosis is based on a combination of cytology, cystoscopy and bioptical mapping (5).
Cytology is highly sensitive in the detection of CIS (over 90%) (13). Positive cytology in the presence of normal cystoscopy should prompt site directed biopsies of the bladder mucosa. When these biopsies are negative, extravesical sites may be a reservoir for CIS, and the evaluation should include upper urinary tract imaging with selective cytology and prostatic urethral biopsy (14). An invasive or papillary lesion must be excluded by cystoscopy (15).
Hexaminolevulinate fluorescence (HAL) cystoscopy had a significantly higher CIS detection rate than white light (WL) cystoscopy and may increase the detection of occult CIS lesions by 20% (16-18). Moreover, Photodynamic diagnosis cystoscopy is more reliable than WL cytoscopy for the follow-up of CIS patients during BCG treatment (19). The sensitivities of most actual urinary tumour markers are disappointing in the diagnosis of CIS (20).
In today's clinical routine, CIS remains a major challenge. Radical cystectomy had represented the best chance of a cure until intravesical BCG therapy was applied in 1976 (21). Numerous studies have supported the efficacy of intravesical BCG in the treatment of CIS and without apparent survival risk for delaying more aggressive

therapy (i.e. radical cystectomy) (4,6,22-28). Intravesical BCG significantly reduces the risk of short and long-term treatment failure compared with intravesical chemotherapy (29-31).

The American Urological Association and the European Association of Urology Clinical Guidelines Panel currently recommends the intravesical instillation of BCG as an initial bladder-sparing approach to treating CIS, after elimination of all visible papillary disease (32). But there is still uncertainty regarding the long-term outcome, optimal number of instillations and dose.

A review of 34 series by Lamm (22), comprising 1354 patients treated with BCG for CIS of the bladder, revealed an average complete response rate of 72%. Nevertheless, on average 28% of patients are refractory to BCG immunotherapy and putting them at risk for disease progression (4). In our series, this rate was slightly less. Some authors have pointed out that the results of BCG therapy are not as good in long-term as in the short term (27,33,34) with life-long risk of progression and upper urinary tract tumors recurrence.

Reported progression rates of CIS varied between 7 and 20% for CIS in the absence of invasive disease (29,35-38). Wolf et al. (7) followed 31 patients for up to 14 years and estimated that 75% had progressed to invasive disease after 10 years and that more patients progressed in stage upon further observation. BCG did not affect the risk of progression in prostate or outside the bladder (2,39). It delays rather than prevents progression (36,40). Takashi et al. found that only patient age was significantly associated with tumor recurrence after BCG therapy (41). However, two other studies found that age was not a risk factor for progression after BCG treatment (10,36). We cofirm the same data. Moreover, the extension of CIS was reported as an independent prognostic factor that could predict progression ($p = 0.020$)(42). The prognostic significance of primary versus secondary CIS has been worried earlier. Different reports suggested either a better (43-45) or a worse (37,46) prognosis of primary CIS. Treatment success was less durable with concomitant cancers (33,36,47).

Several investigators have pointed out that response to BCG therapy is an important factor for prognosis (10,42,48,49) for recurrence or disease progression. Biological markers were well studied. Positive expression for both p53 and p21 puts patients with bladder CIS at the greatest risk of bladder cancer recurrence ($p= 0.022$), progression ($p= 0.042$), and, most importantly, cancer-specific survival ($p=0.031$) (50). In the other side, Ovesen et al. (44) found that the absence of p53 nuclear accumulation after BCG was a good prognostic sign. Loss of E-cadherin expression in patients with CIS with and without NMIBC predicts disease recurrence, disease progression, and bladder cancer-specific death. This condition may represent a biologically more aggressive cancer, requiring early definitive therapy (51).

Although anti-tumor effects and adverse effects may vary depending on the types of BCG strains (52), instillation at a dose of 75 mg once weekly for 6 weeks has been established as the standard administration method of BCG (Pasteur strain) in Tunisia (53). Lamm noted an average CR rate of 72% in studies of the effects of various BCG strains upon CIS (54).

While 30-40% of patients do not respond to one course of six instillations, half of these still achieve a complete response after an additional course of six instillations (36). Maintenance BCG has been shown to favorably affect the rate of progression or need for cystectomy (55,56). Consequently, the treatment guideline in CIS patients is maintenance BCG (57,58).

Despite good clinical efficacy, intravesical BCG instillation raises frequent and various adverse effects (especially local adverse reactions) (47,59). Akaza et al. (23) reported bladder irritation symptoms in 69%, fever in 43.7% and macroscopic hematuria in 31%. Infrequent but severe adverse effects have also been reported (59). In the persesent series, no severe complications were reported.

Disease recurrence and progression including the upper urinary tract and prostate could occur even a long time after BCG therapy and should thus be carefully considered (42).

In case of BCG-refractory or BCG-failing CIS, cystectomy is the treatment of choice (60). However, its social and financial costs are high, and there are patients who will refuse it as in our series. Treatment with intravesical hyperthermia and MMC appears a safe and effective treatment. The initial CR response rate was 92%, which remains approximately 50% after 2 years (61). We didn't have any experience with this therapy.

Several limitations and weakness have been noted in this study and should be discussed.

Data were retrospective and selection bias had to be considered, as the selection towards patients who received full BCG instillations and were followed for long period. We have presented the results of BCG treatment of 47 patients with CIS and long follow-up period. Most other reports (34,36,44,48) either had a smaller number of patients or a shorter follow-up period. Another advantage of our study is that it was unselected, with all BCG-treated CIS patients from four geographical regions being included.

Exclusion biais was not significant and only 3 patients were not included in our study.

Detection biais was a real problem in the present series. Although, urinary cytology is the standard for diagnosis, it remains under practiced in our hospitals. This may be due to lack of experienced cytologist and technical difficulties in sampling and lecture. We point on that cytology must be more and more practiced in our routine practice as recommended by international societies. Thus we may develop our own experiences and competent framework.

CONCLUSION

Our study supports current evidence that BCG therapy with maintenance is an effective and safe therapy for CIS. Our data suggest that patients with primary CIS and CIS associated with NMIBC have similar 5-year outcomes. Secondary CIS may have a worse outcome but we didn't find significant prognostic factor.

Disease recurrence and progression including extravesical involvement (upper urinary tract and prostate) must be carefully monitored over the long-term after BCG therapy.

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