Bacillus Calmette-Guerin infection following intravesical instillation: does the strain matter?

BCGites dans les suites d'instillations intravésicales : la souche de BCG importe-t-elle ?

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Mots clés : BCG ; cancer de vessie

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RÉSUMÉ

Objectifs. La BCG-thérapie est le traitement standard des tumeurs de vessie n'infiltrant pas la musculuse. Aucune différence de tolérance entre les différentes souches de BCG n'a été rapportée.

Patients et méthodes. Une étude multidisciplinaire rétrospective française a été menée entre janvier 2013 et décembre 2016 pour identifier les cas de BCGites et comparer leur présentation clinique selon la souche utilisée.

Résultats. Quarante patients ont été inclus : (BCG RIVM 28 ; autres souches 8 ; inconnue 4). Les patients traités avec BCG-RIVM présentaient plus de miliaries pulmonaires (71,4 % vs 12,5 %, $p=0,005$), moins de chocs septiques (3,6 % vs 50 %, $p=0,003$), des taux de transaminases plus bas (moyenne AST 65 vs 264 U/l, $p=0,001$) et avaient moins recours à la réanimation (7,1 % vs 62,5 %, $p=0,003$). L'évolution était superposable entre les deux groupes.

Conclusion. La souche de BCG pourrait influencer la fréquence et la sévérité d'une BCGite.

ABSTRACT

Purpose. Intravesical BCG is the standard treatment of non-muscle-invasive bladder cancer. No difference has yet been reported in the safety profiles of the various BCG strains.

Methods. A nationwide multidisciplinary retrospective survey was conducted between January 2013 and December 2016 to identify cases of BCG infection and differentiate them based on the type of BCG strain used.

Results. Forty patients were identified (BCG RIVM 28; other strains 8; unknown 4). Patients treated with BCG RIVM were less severely ill, with fewer occurrences of septic shock (3.6% vs 50%, $p=0.003$) and ICU admission (7.1% vs 62.5%, $p=0.003$). A higher frequency of pulmonary miliaries (71.4% vs 12.5%, $p=0.005$) but lower transaminase levels (mean AST 65 vs 264 U/l, $p=0.001$) were observed in these patients. No difference in terms of recovery was reported.

Conclusion. The type of BCG strain could correlate with the frequency and severity of subsequent BCG infections.

INTRODUCTION

Intravesical instillation of bacillus Calmette-Guerin (BCG) is the most effective adjuvant treatment of non-muscle invasive bladder cancer (NMIBC) after transurethral resection of the bladder (TURB) [1-7]. Side effects are usually mild and transient, although localized (1%) or systemic (<1% to 4.7%) mycobacterial infections can occur [8-10]. These often lead to early treatment discontinuation, and thus negatively impact the disease course [11]. Among the eight available BCG-marketed strains, BCG Connaught, TICE, and *Rijksinstituut voor Volksgezondheid en Milieuhygiene* (RIVM) are the most commonly used. Data is conflicting regarding the strains' efficacy rates, and to date no difference has been identified in their safety profiles [12-17].

We performed a multicenter nationwide study to report on the clinical spectrum and therapeutic management of patients presenting with BCG infection following immunotherapy for NMIBC, in the context of a change of supplier (stockout of BCG Connaught at year end 2012, changed for BCG RIVM). We aimed to assess a potential link between the type of BCG strain and subsequent BCG infections.

METHODS

Patients

Between December 2013 and April 2016 three unrelated medical institutions noticed an unusually high number of BCG infections occurring over a short period of time in patients who received BCG intravesical instillation after TURB for NMIBC. Subsequently, thanks to collaborative networks (Association Française d'Urologie,

Société de Pathologie Infectieuse de Langue Française, Société de Pneumologie de Langue Française, Amicale des Jeunes Internistes, Centres de Lutte Antituberculeuse), a nationwide retrospective survey was conducted to identify additional patients diagnosed with BCG infection over the same time period. This study complied with the Declaration of Helsinki and the French legislation regarding observational studies (Loi Huriet-Sérusclat 88-1138 and its subsequent amendments) in force at the time of the study.

Definition of BCG infection

BCG infections were defined as more than three days of high-grade fever and systemic and/or local manifestations (other than voiding symptoms) with no other plausible alternative diagnosis [9], occurring after BCG instillation for bladder cancer. Neither microbiological nor histological confirmation was needed to assess the diagnosis of BCG infection.

Assessments, outcome, and response to therapy

Collected data included demographic, clinical, biological, radiological, microbiological, and histological findings at the time of diagnosis and during follow-up. Recovery was defined as the resolution of all symptoms and biological abnormalities attributable to the BCG infection.

Statistical analysis

Descriptive statistics included the mean (SD) or median (range), as appropriate, for continuous variables, and frequency (percentage) for categorical variables. In each facility, the incidence rates were calculated using the ratio of the number of cases to the number of patients treated with BCG RIVM during the study period. Patient subsets were differentiated based on the type of BCG strain used. Univariate analysis

included the chi-square or Fisher's exact test, as appropriate, to compare categorical variables and the non-parametric Mann-Whitney test to compare continuous variables. All tests were performed using GraphPad Prism version 7.0b 2016. A $p<0.05$ was considered significant.

RESULTS

Patients

When BCG Connaught stopped being marketed in France, 14 cases of RIVM-related BCG infections occurred in three unrelated hospitals (three in Cochin hospital, six in Saint-Louis hospital, five in Perpignan's Medipole clinic) with incidence rates of 7.3%, 14.6%, and 4.5% in these three facilities, respectively. Unlike the other two medical facilities, the BCG TICE strain was used concomitantly with the RIVM strain in the Saint-Louis hospital. No BCG infection was reported in the 19 patients (32% of all patients) treated with this strain in that hospital over the same time period.

Twenty-six additional cases were identified thanks to the nationwide survey, among which 14 had been treated with BCG RIVM, eight with other strains (BCG Connaught, $n=5$; BCG TICE, $n=2$; BCG SSI, $n=1$), and four with unknown strains. Hence, 28 patients were included in the BCG RIVM group and eight in the non-BCG RIVM group (Table 1).

Baseline characteristics

Median age at diagnosis was 69 years (IQR 14,3). Thirty-eight (95%) patients were male and 25 (89.2%) had high-grade NMIBC. General characteristics were identical in both groups, including the causes of underlying immunosuppression, the number of

previous BCG instillations, and the traumatic nature of the last instillation (Table 1).

The clinical presentation at disease onset was highly heterogeneous with various TB presentations: miliary (n=21), hepatitis (n=8), tissue abscess (n=3), isolated fever (n=3), vascular involvement (n=2), pelvic collection (n=2), and adrenal necrosis (n=1). Fever was constant, and 19 patients (47.5%) had respiratory symptoms. Whole-body CT scans were performed on all patients: pulmonary miliary lesions were observed in 22 (55%) patients, while other thoracic radiological features included pulmonary embolism (n=3), mediastinal lymphadenopathy (n=2), alveolar opacity (n=4), and pulmonary nodule (n=1). Patients treated with BCG RIVM were less severely ill, with fewer occurrences of organ failure (10.7% vs 62.5%, $p=0.006$) and septic shock (3.6% vs 50%, $p=0.003$), fewer ICU admissions (7.1% vs 62.5%, $p=0.003$) and a lower use of vasoactive drugs (3.6% vs 42.9%, $p=0.018$). Patients treated with BCG RIVM more often presented with pulmonary miliary (71.4% vs 12.5%, $p=0.005$) but lower transaminase levels (mean AST 65 vs 264 U/l, $p=0.001$ and ALT 76 vs 142 U/l, $p=0.009$) than those treated with other strains.

Microbiological and histological findings

Overall, BCG infections were microbiologically confirmed in 11/40 (27.5%) patients (Table 2) and were less frequent in the BCG RIVM group (17.9% vs 62.5%, $p=0.024$). Respiratory samples were poorly sensitive. In patients presenting with cytopenia (n=2) or ^{18}F -FDG PET/CT bone marrow involvement (n=1), medullary culture was contributive. All patients with positive PCR on tissue biopsies (2/5, 40%) also had positive cultures on the same samples. Other PCR tests (blood, n=1; stools n=1)

enabled the diagnosis for two patients who otherwise had no positive microbiological test.

Histological confirmation of the BCG infection was obtained in 12 (75%) patients out of the 16 who underwent a biopsy. Overall, 14/18 biopsies performed led to the identification of epithelioid and gigantocellular granuloma. Besides bronchial biopsies (never contributive), all biopsy sites showed a good diagnostic sensitivity (ranging from 50% to 100%) for the diagnosis of BCG infection (Table 2).

Treatment and outcomes

The management of patients was highly heterogeneous (Table 3) but comparable between groups. Overall, the combination of ethambutol (discontinued after two months), rifampicin, and isoniazid for six months was the most frequently prescribed regimen (26/40 patients, 65%).

Due to the severity of the initial clinical presentation (n=16) or to general symptoms refractory to antimicrobial therapy (n=5), 21 patients (52.5%) received an adjuvant treatment with prednisone (starting dose up to 1 mg/kg/day with gradual tapering) for a mean 2.6 months (range 0.25 - 8 months), among which six (29%) experienced steroids-related adverse events.

Overall, there was no difference in treatment outcomes between strains (Table 3). Thirty-four patients (82.5%) recovered from the BCG infection and two patients died (NMIBC progression and BCG-related respiratory failure despite steroid treatment, a single patient each).

DISCUSSION

BCG infection is a well-known complication after intravesical instillation for NMIBC. Yet, to our knowledge, the present study is the first to suggest that the type of BCG strain could correlate with the frequency and severity of subsequent BCG infections. Herein, rates of BCG infection were high in three facilities that used BCG RIVM and, overall, BCG RIVM-related infections were less severe than those occurring in patients treated with non-RIVM strains. Nevertheless, the overall mortality of this study is similar to that reported in the literature [9].

This work was initiated by several unrelated physicians who were struck by the high incidence of BCG infections occurring in their facility over a short period of time. Of note, all of the 14 initial cases occurred with the BCG RIVM strain despite the concomitant use of batches of BCG TICE in Saint-Louis Hospital, and no other case was reported after BCG RIVM stopped being used in Cochin hospital (September 2014).

We believe that host characteristics are not the main risk factor in our series as the BCG RIVM group was not massively immunosuppressed and because more than four weeks was observed between transurethral resection and BCG instillation in all cases. The four different batch numbers identified among patients with RIVM-related BCG infection seem to rule out the hypothesis that a particular batch could be incriminated in these consecutive cases. As BCG RIVM comes with its own bladder catheter and as macroscopic hematuria was reported in 42.9% of cases reported in the present series (vs 1% to 34% in previous series [8-10]), local trauma might also be a plausible explanation. Of note, the decision of the BCG RIVM's supplier to change the instillation device in February 2016 gives credit, at least partly, to this assumption.

Our study has a low sample size and limitations inherent to its retrospective design, namely missing data, loss to follow-up, and the lack of standardized diagnostic and therapeutic procedures. As there is no proper code for the diagnosis of BCG infection in the medical information system database, it is also likely that our study was not a comprehensive survey of all incident cases of BCG infection occurring in France over the study period.

Yet, this data arising from complementary collaborative networks supports the implementation of both basic and clinical studies to better decipher the interplay between BCG strains (and instillation devices) and patient outcomes. Hence, prospective studies are needed, especially as BCG Connaught production resumed at the end of 2016. As the batch number was reported in the medical files of only 15/40 patients of the present series, our findings underline the opacity of our current drug traceability system, which should be considerably improved.

CONTRIBUTION OF AUTHORS

LIL, FS, and MG designed the protocol and wrote the first draft of the article; LIL, FS, NDC, OB, NV, XA, OL, MR, AB, and OL were involved in data collection and interpretation. LIL performed the statistical analyses. All authors were involved in critically revising the article and approved the final version to be submitted for publication.

DECLARATION OF INTERESTS

The authors declare no competing financial nor personal interests.

ETHICAL APPROVAL

This study complies with the standard recommendations for clinical trials, the Declaration of Helsinki, and the French legislation regarding observational studies in force at the time of the study (Loi Huriet-Sérusclat 88-1138 and its subsequent amendments).

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Table 1. Baseline characteristics of patients according to the type of BCG strain**Tableau 1.** Caractéristiques initiales des patients selon la souche de BCG reçue

	Total n=40	BCG-RIVM n=28	Non-BCG-RIVM n=8	<i>p</i> value
General characteristics				
Sex (Male), n (%)	38/40 (95)	26/28 (92.9)	8/8 (100)	0.99
Age (years), mean (SD)	68/40 (9.4)	67/28 (10.4)	69/28 (9.8)	0.68
Immunosuppression, n (%)	12/40 (30)*	8/28 (28.6%) [†]	2/8 (25) [†]	0.99
High-grade NMIBC, n (%)	25/28 (89.3)	18/20 (90)	5/5 (100)	0.99
Number of previous instillations (mean) / data collected	3-3/38	2.5-3.3/26	2.9-3.5/8	0.12-0.82
Length between TUVR and BCG instillation (days), median/data collected [IQR]	77/22 [43-83]	72.4/18 [42- 73]	105/2 [90-120]	0.06
Recent urinary tract infection	5/34 (20.8)	4/23 (17.4)	1/7 (14.3)	0.99
Length between the last instillation and onset of symptoms (days), median [IQR]	1/39 [0-5]	1/28 [0-4]	2.5/8 [0-285]	0.58
<1 month, n (%)	35 (87.5)	25 (89.3)	6 (75)	0.22
>3 months, n (%)	4 (10)	2 (7.1)	2 (25)	
Traumatic instillation, n (%)	18/37 (48.6)	12/27 (42.9)	3/6 (50)	0.99
Symptoms and presentation, n (%)				
Fever	40/40 (100)	28/28 (100)	8/8 (100)	1
Organ failure	8/40 (20)	3/28 (10.7)	5/8 (62.5)	0.006
Septic shock	5/40 (12.5)	1/28 (3.6)	4/8 (50)	0.003
Dyspnea	15/39 (38.5)	11/28 (39.3)	3/7 (39.3)	0.43
Cough	11/39 (28.2)	9/27 (33.3)	2/8 (25)	0.99

Expectoration	3/38 (7.9)	1/27 (3.7)	1/7 (14.3)	0.37
Oxygen therapy	10/38 (26.3)	6/27 (22.2)	4/7 (57.1)	0.16
Urinary tract symptoms	10/39 (25.6)	6/27 (22.2)	2/8 (25)	0.99
Cutaneous involvement	6/38 (15.4)	2/28 (7.1)	3/7 (42.9)	0.04
Splenomegaly	6/40 (15)	2/28 (14.3)	2/8 (25)	0.6
Hepatomegaly	6/40 (15)	4/28 (7.1)	3/8 (37.5)	0.06
Icterus	2/40 (5)	0/28 (0)	2/8 (25)	0.04
Laboratory findings, mean (SD)				
C-reactive protein (mg/l)	96.6/35 (69)	90/25 (61)	170/6 (94)	0.53
AST (U/l)	105.1/36 (128)	65.6/25 (55)	264.1/7 (202)	0.001
ALT (U/l)	97/36 (94)	75.9/25 (63)	203/7 (128)	0.009
Alkaline phosphatase (U/l)	243.1/32 (245)	196.1/23 (147)	443.5/6 (419)	0.19
GGT (U/l)	271/37 (283)	227.5/25 (211)	437.3/8 (434)	0.15
Bilirubin (μmol/l)	16.6/34 (23)	12.1/22 (5)	34.2/8 (42)	0.73
Radiological findings, n (%)				
Miliary	22/40 (55)	20/28 (71.4)	1/8 (12.5)	0.005
Hepatic involvement	8/39 (20.5)	2/27 (7.4)	4/8 (50)	0.016
Pleural effusion	5/40 (12.5)	4/28 (14.3)	0/8 (0)	0.99
Prostatic involvement	4/39 (10.3)	3/27 (11.1)	0/8 (0)	0.99
Renal involvement	4/39 (10.2)	2/27 (7.4)	2/8 (25)	0.22
Pericardial effusion	3/40 (7.5)	2/28 (7.1)	1/8 (12.5)	0.54
Vascular involvement	2/39 (5.1)	2/27 (7.4)	1/8 (12.5)	0.54
Bone involvement	1/39 (2.6)	0/27 (0)	1/8 (12.5)	0.23

Pathological findings

Biopsy performed, n (%)	16/39 (41)	8/27 (29.6)	5/8 (62.5)	0.12
Positive biopsy/biopsy performed, %	75	50	100	0.11
Microbiological documentation, n (%)	11 (27.5)	5 (17.9)	5 (62.5)	0.02

* diabetes (n=7), methotrexate and prednisone treatment for rheumatoid arthritis (n=1), chronic kidney failure with glomerular filtration rate <30 ml/min (n=2), HIV infection (CD4 >200/mm³) (n=1), myelodysplastic syndrome (n=1)

+ diabetes (n=4), methotrexate and prednisone treatment for rheumatoid arthritis (n=1), chronic kidney failure with glomerular filtration rate <30 ml/min (n=2), HIV infection (CD4 >200/mm³) (n=1)

+ diabetes (n=2)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BCG: Calmette and Guérin bacillus; GGT: gamma-glutamyl transpeptidase; IQR: interquartile range;

NMIBC: non-muscular invasive bladder cancer; RIVM: *Rijksinstituut voor Volksgezondheid en Milieuhygiene*; SD: standard deviation; TURV: transurethral vesical resection.

Table 2. Microbiological and pathological findings

Tableau 2. Données microbiologiques et anatomopathologiques

[illegible]

Liver	6 (15)	5 (83)	2 (7.1)	1 (50)	3 (37.5)	3 (100)
Abdominal mass	2 (5)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Lymph nodes	2 (5)	2 (100)	1 (3.6)	1 (100)	1 (12.5)	1 (100)
Cutaneous	2 (5)	1 (50)	1 (3.6)	0 (0)	1 (12.5)	1 (100)
Bronchial	3 (7.5)	0 (0)	3 (10.7)	0 (0)	0 (0)	0 (0)
Transbronchial	1 (2.5)	1 (100)	1 (3.6)	1 (100)	0 (0)	0 (0)
Bone marrow	1 (2.5)	1 (100)	0 (0)	0 (0)	1 (12.5)	1 (100)
Ovaries (adnexectomy)	1 (2.5)	1 (100)	1 (3.6)	1 (100)	0 (0)	0 (0)

PCR: polymerase chain reaction

Table 3. Patient management and outcome according to the type of BCG strain

Tableau 3. Prise en charge et devenir des patients selon la souche de BCG

	Total n=40	BCG-RIVM n=28	Non-BCG-RIVM n=8	p value
Patient care				
Length of hospitalization (days), median [IQR]	23.6 [6.5-18.5]	14 [7-17.5]	25.5 [6.5-99]	0.18
Need for intensive care, n (%)	7/40 (17.5)	2/28 (7.1)	5/8 (62.5)	0.003
Orotracheal intubation, n (%)	4/39 (10.3)	2/28 (7.1)	2/7 (28.6)	0.17
Use of vasoactive amines, n (%)	4/39 (10.3)	1/28 (3.6)	3/7 (42.9)	0.02
Treatment regimen				
Antimycobacterial therapy				0.29
IR, n (%)	8/40 (20)	6/28 (21.4)	0/8 (0)	
IRE, n (%)	25/40 (62.5)	17/28 (60.7)	7/8 (87.5)	
Other antibiotic combination, n (%)	7/40 (17.5)	5/28 (17.8)	1/8 (12.5)	
Duration of antimicrobial therapy (months), mean (SD)	5.9 (2.4)	5.7 (2)	6.6 (3)	0.16
Use of glucocorticoids, n (%)	21/40 (52.5)	15/28 (53.6)	5/8 (62.5)	0.71
Duration of glucocorticoid therapy (months), mean (SD)	2.6 (2.2)	2.6 (2.4)	3.1 (1.9)	0.62
Follow-up CT scan, n (%)	N=23	N=17	N=4	0.51
Stable or worse	5/23 (21.7)	5/17 (29.4)	0/4 (0)	
Improved	13/23 (56.5)	9/17 (52.9)	2/4 (50)	
Normalized	5/23 (21.7)	3/17 (70.1)	2/4 (50)	
Last follow-up				
Time between BCG and last follow-up (days), median [IQR]	478 [204-496]	271 [188-476]	137 [45-360]	0.09
Recovery from BCG infection, n (%)	34/40 (85)	23/28 (82.1)	7/8 (87.5)	0.59
Death, n (%)	2/40 (5)	1/28 (3.6)	1/8 (12.5)	
Resumption of urological treatments, n (%)	17/34 (51.5)	10/22 (45.4)	5/8 (62.5)	0.42
Need for cystectomy, n (%)	6/30 (20)	4/22 (18.2)	2/5 (40)	0.30
Palliative care, n (%)	5/31 (16.1)	2/21 (9.1)	1/7 (14.3)	0.99
Remission of malignancy, n (%)	17/30 (58.6)	13/21 (61.9)	3/5 (60)	0.99

BCG: Calmette and Guérin bacillus; IQR: interquartile range; IR: isoniazid and rifampicin; IRE: isoniazid, rifampicin, and ethambutol; RIVM: *Rijksinstituut voor Volksgezondheid en Milieuhygiene*; SD: standard deviation.