J Clin Tuberc Other Mycobact Dis 19 (2020) 100149

Contents lists available at ScienceDirect

J Clin Tuberc Other Mycobact Dis

journal homepage: www.elsevier.com/locate/jctube

Intravesical Bacillus Calmette-Guérin (BCG) treatment's severe complications: A single institution review of incidence, presentation and treatment outcome

R. Waked[a,*], J. Choucair[b], N. Chehata[a], E. Haddad[a], G. Saliba[a]

[a] Department of Infectious Diseases, Faculty of Medicine, Saint Joseph University, Damascus street, PO BOX 11-5076, Riad El Solh, Beirut 1107 2180, Lebanon
[b] Coordinator of the Infectious Diseases department, Saint Joseph University, Beirut, Lebanon

ARTICLE INFO

Keywords:
Mycobacterial infection
Intravesical Bacillus Calmette-Guérin
Bacillus Calmette-Guerin
Urothelial bladder cancer
Severe complication
Treatment protocol

ABSTRACT

Objectives: Intravesical Bacillus Calmette-Guérin (BCG) treatment for superficial bladder cancer is interrupted in approximatively 8% of cases as a result of complications. The objective is to report the severe related complications of Bacillus Calmette-Guérin (BCG) following an intravesical instillation for bladder tumor encountered at our institution for the past 5 years.

Methods: Medical records of a tertiary teaching hospital, located in Beirut, Lebanon, were retrospectively analyzed from June 2014 to June 2019 searching for severe related complications of BCG. A comprehensive review of articles on this subject was conducted.

Results: The incidence of severe systemic adverse events related to BCG instillation was 1.5% (5 out of 332 patients). A total of five patients were found to have a severe BCG related complication, with fever, chills, and irritative urinary signs being the most frequent symptoms. All patients received antituberculosis therapy (Isoniazid, Rifampin and Ethambutol). Two were put on add-on corticosteroids. Three patients had a computed tomography scan image in favor of an infection. Two patients had a favorable outcome, three patients died.

Conclusion: BCG severe adverse events were mostly seen in patients with a traumatic instillation. Treatment used at our institution was similar to most cases reported in the literature. A standardized diagnostic and treatment approach should be implemented to help physicians tackle these life-threatening complications.

1. Background

Ranked ninth most commonly diagnosed cancer and thirteenth leading cause of cancer deaths worldwide, bladder tumors caused 165,000 deaths worldwide in 2012 [1]. After transurethral resection, 61% of non-muscle invasive bladder tumors (NMIBT) recur [2]. This high percentage requires an adjuvant treatment [2]. In 1990, the US Food and Drug Administration approved the use of intravesical bacillus Calmette-Guérin (BCG) for the treatment of superficial bladder cancer as an adjuvant therapy [3]. BCG is a live, attenuated strain of Mycobacterium bovis (M. bovis) [3]. The meta-analyses of randomized trials have proved the efficacy of intravesical BCG treatment to reduce local recurrences and the risk of progression to muscle after trans-urethral resection [4,5]. The precise mechanism by which BCG acts is unknown, but a local granulomatous inflammatory reaction, partly due to a T-cell–mediated immunity response, is thought to play a role [6].

However, this treatment is interrupted in approximatively 8% of cases as a result of complications. These complications, that may arise, can appear either in conjunction or months after BCG instillation [7]. The most frequent local side effects are chemical cystitis, bacterial cystitis, urinary frequency, macroscopic hematuria, urinary incontinence. The most frequent systemic side effects are general malaise and fever. Sepsis rarely occurs [8]. Due to the wide range of presentations and potential severity, these complications pose a challenge for the clinician.

In the present study, we aimed at analyzing patients who underwent intravesical BCG instillation for a NMIBT at our institution during a 5-year period. Our goal was to determine the incidence, presentation, risk factors, diagnosis, treatment and outcome of BCG's severe complications after receiving intravesical treatment. A brief review is also presented, with focus on risk factors, means of prevention, and therapeutic approach.

Abbreviations: BCG, Bacillus Calmette-Guérin; NMIBT, Non-muscle invasive bladder tumors; M. bovis, Mycobacterium bovis; TST, Tuberculin skin testing; PCR, Polymerase chain reaction; CT scan, Computed tomography scan; COPD, Chronic obstructive pulmonary disease; DNA, Deoxyribonucleic acid

* Corresponding author.
E-mail address: ramiwaked12@hotmail.com (R. Waked).

https://doi.org/10.1016/j.jctube.2020.100149

2405-5794/ © 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

2. Methods

This study was performed at a university hospital in Beirut, Lebanon. We retrospectively assessed our electronic medical records for the past 5 years (June 2014 to June 2019) searching for "BCgite" and "bécégite" with the following the international classification of diseases and related health problems (ICD)-10 in the medical record: T806 associated to Y580. We identified a total of five cases who received intravesical BCG instillations (BCG-medac imported from Germany, BCG bacteria seed RIVM derived from seed 1173-P2 2×10^8 to 3×10^9 viable units, 50 ml) as adjunctive treatment of superficial bladder cancer throughout this period and who developed a confirmed severe BCG related complication. The intravesical BCG protocol used at our hospital follows the one stated in the "Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma" [9]. The following variables were retrospectively assessed by medical record review using a standardized data collection form: sex, age, the pathologic TNM staging of bladder cancer at diagnosis, overall number of BCG instillations, time interval between the last BCG instillation and the diagnosis of the complication, symptoms and type of infection, histologic and microbiologic findings, treatment and outcome.

A BCG infection was defined, after reviewing several articles [10–12], as the presence of:

- Clinical symptoms consistent with active tuberculosis infection (fever of 39° C or more for at least 48 h, night sweats, chills) or infection of a specific organ (hepatitis, pneumonitis, osteomyelitis, arthritis…), following at least one instillation of intravesical BCG, in the absence of a well confirmed alternative diagnosis

  And

  A newly positive tuberculin skin testing (TST) read after 72 h (with minimum induration of 10 mm in diameter) without a history of BCG vaccination or positive TST, and/or a microbiologic evidence of infection (positivity for *Mycobacterium tuberculosis* complex by culture or by polymerase chain reaction [PCR] assay) and/or a histopathologic evidence of mycobacterial infection (inflammation with caseating granulomas in biopsy specimens). A severe BCG related complication was defined as systemic symptoms (fever and chills) severe enough to discontinue BCG immunotherapy and requiring prompt antituberculosis treatment.

Authorization by the ethical committee of the Saint-Joseph University, Beirut, Lebanon for data processing and publication was obtained. A written informed consent was obtained from the patient or the next of kin for publication of this article.

3. Results

The total number of patients receiving BCG instillations during that period (June 2014 to June 2019) in our tertiary teaching hospital was 332. The incidence of severe systemic adverse events related to BCG instillation was around 1.5% (5 out of 332 patients).

In the following section, and after de-identification of specific patients' information, the cases encountered at our institution are presented (details in Table 1):

Patient 1 was a 72-year-old man, known to have a high-grade papillary carcinoma pT1pNxpMx. He already received 4 intravesical BCG instillations. He was complaining of fever, dysuria and urinary frequency 4 weeks after starting his weekly intravesical BCG treatment. His urine culture was negative (no mycobacterial culture was done). Chest and abdominal CT scan did not show any abnormality. He was started on Rifampin 600mg per day Ethambutol 400mg every 8 h and Isoniazid 300 mg per day soon after having a newly positive TST (25 mm of induration). He never received a BCG vaccine nor had a history of positive TST. The patient received 2 months of antibiotics resulting in the resolution of symptoms.

Patient 2, a 69-year-old man, was known to have an invasive papillary carcinoma pT2apNxpMx. He was treated with BCG instillations. He presented with fever, dysuria and urinary frequency 7 months after his first dose of intravesical BCG. He received his 10^{th} BCG instillation one week before the symptoms' started. Urine culture and TST came negative. Liver enzymes were normal, and no pulmonary involvement was identified on the chest CT scan. Bladder histology showed granulomatous inflammation. The patient received Rifampin 600mg per day, Ethambutol 400mg every 8 h and Isoniazid 300mg per day. He was put on methylprednisolone 40mg q24h for one week then he was discharged on prednisone tapering dose. The patient died after 4 months due to progression of his cancer.

Patient 3, an 84-year-old man, had a high-grade papillary carcinoma pT1pNxpMx. He developed chills and obstructive urinary signs at his 12th BCG instillation. His urine culture and TST were negative. There was no elevated liver enzymes nor pulmonary involvement. He was empirically treated with Levofloxacin 500mg daily for one week. Subsequently, the histology of his last cystoscopy showed a granulomatous inflammation compatible with a BCG infection. This patient was transferred to another institution where he was put on anti-tuberculous treatment (Rifampin 600mg per day Ethambutol 400mg every 8 h and Isoniazid 300mg per day), but his state deteriorated, and he passed away one month later.

Patient 4, a 71-year-old women, had an invasive papillary carcinoma pT2apNxpMx. She was admitted to the intensive care unit because she developed hypotension, fever, acute kidney injury and decreased level of consciousness. She was intubated and put on vasopressors. The patient had already received several BCG instillations (eight instillations) with the last dose received two days before her admission to the intensive care unit. A CT scan of the chest, abdomen and pelvis did not show any sign of infection. A urinary PCR was positive for Mycobacterium bovis. Methylprednisolone 40mg every 8 hours for ten days, Rifampin 600mg per day, Ethambutol 400mg every 8 h and Isoniazid 300mg per day were started. Aplastic anemia and elevated liver enzymes (10 times of normal upper limit) appeared ten days after treatment instauration. Rifampin and Isoniazid were switched to Amikacin (target peak and trough therapeutic levels for amikacin were 15–20 mg/L and <5 mg/L, respectively) and Moxifloxacin 400mg per day. Histology of the bone marrow showed inflammatory granulomas in favor of a disseminated BCG infection. The patient died two weeks after admission due to a cardiac arrest following a confirmed macrophage activation syndrome.

Patient 5 was a 58-year-old man with a low-grade papillary carcinoma pT1pNxpMx. He was admitted to the hospital for chills, fever, irritative urinary symptoms and weight loss. He was icteric. His liver function tests were elevated (4 times upper limit). He had already received several intravesical BCG injections (20 doses). He received his last BCG instillation two weeks before his admission to the hospital. Urine cultures returned negative (ordinary and mycobacterial cultures). PCR on a urine sample was positive for Mycobacterium Bovis. A CT scan of the abdomen and pelvis showed a circumferential parietal thickening of the bladder with infracentimetric retroperitoneal lymph nodes. Chest imaging did not show any abnormality. The patient's liver enzymes improved after intravenous hydration. He was started on Rifampin 600mg per day, Ethambutol 400mg every 8h and Isoniazid 300mg per day, with close liver enzymes monitoring. He received 6 months of antituberculosis therapy, resulting in the resolution of symptoms.

4. Discussion

Bacillus Calmette-Guérin immunotherapy remains a very important adjuvant therapy following a transurethral resection of a non-muscle-

Table 1
Overview of clinical characteristics, diagnostic and therapeutic approaches, treatment, and outcomes for five cases of systemic BCG related complications.

	Age (years)	Gender	Symptoms	Underlying conditions	Pathologic TNM[1] staging of bladder cancer at diagnosis	BCG[2] instillations before symptoms	Time between last BCG[2] dose and onset of symptoms (days)	Type of BCG[2] complication	Radiology
Patient 1	72	Male	Fever Dysuria Urinary frequency	COPD[3] Hypertension Dyslipidemia	High grade papillary carcinoma pT1pNxpMx	4	Immediately after last BCG[2] instillation	Systemic without organ involvement	Chest and abdominal CT[4]: no relevant abnormality
Patient 2	69	Male	Fever Dysuria Urinary frequency	Diabetes Hypertension COPD[3] Chronic Kidney Disease stage 3	Invasive papillary carcinoma pT2apNxpMx	10	7	Urinary	Chest CT[4]: no relevant abnormality Uroscan: circumferential parietal thickening of the bladder with lateral aortic and iliac lymph nodes
Patient 3	84	Male	Chills Obstructive urinary signs	Non-significant	High grade papillary carcinoma pT1pNxpMx	12	Immediately after last BCG[2] instillation	Urinary	Uroscan: circumferential parietal thickening of the bladder without any enlarged lymph node
Patient 4	71	Female	Hypotension Fever decreased level of consciousness	Hypertension	Invasive papillary carcinoma pT2apNxpMx	8	2	Systemic with bone marrow infiltration and macrophage activation syndrome	CT[4] scan of the chest, abdomen and pelvis: No relevant abnormality
Patient 5	58	Male	Chills Fever Irritative urinary signs Weight loss Jaundice	COPD[3] Alcoholic Hypertension Dyslipidemia	Low grade papillary carcinoma pT1pNxpMx	20	14	Systemic with urinary involvement	CT[4] scan of the abdomen and pelvis showed a circumferential parietal thickening of the bladder with infracentimetric retroperitoneal lymph nodes

	Traumatic BCG instillation	Microbiology and TST[5]	Histology	Antibiotics and duration of treatment	Steroids	Outcome
Patient 1	Yes	. Negative urine culture . TST[5] 25 millimeters	Not performed	2 months of Rifampin 600mg per day Ethambutol 400mg every 8 hours and Isoniazid 300mg per day	Not used	Resolution of BCG[2] disease
Patient 2	Yes	. Negative urine culture and TST[5]	Granulomatous inflammation in bladder	4 months of Rifampin 600mg per day Ethambutol 400mg every 8 hours and Isoniazid 300mg per day	methylprednisolone 40mg per day for one week the prednisone 40mg tapering for 2 months	Death due to tumor progression
Patient 3	Yes	. Negative urine culture and TST[5]	Granulomatous inflammation in bladder	Levofloxacin 500mg per day for one week then one month of Rifampin 600mg per day Ethambutol 400mg every 8 hours and Isoniazid 300mg per day	Not used	Death
Patient 4	Not known	PCR[6] on urine positive for M. Bovis[7]	Inflammatory granulomas in bone marrow	Ten days of Rifampin 600mg per day, Ethambutol 400mg every 8 hours and Isoniazid 300mg per day. Rifampin and isoniazid were switched to Amikacin (target peak and trough therapeutic levels for amikacin were 15-20 mg/L and <5 mg/L, respectively) and Moxifloxacin 400mg/day (aplastic anemia and elevated liver enzymes (10 times of normal upper limit) developed)	Methylprednisolone 40mg every 8 hours for 10 days	Death due to cardiac arrest

(*continued on next page*)

Table 1 (*continued*)

	Age (years)	Gender	Symptoms	Underlying conditions	Pathologic TNM[1] staging of bladder cancer at diagnosis	BCG[2] instillations before symptoms	Time between last BCG[2] dose and onset of symptoms (days)	Type of BCG[2] complication	Radiology
Patient 5	Yes	PCR[6] on urine positive for M. Bovis[7] Negative urine culture	Not performed	6 months of Rifampin 600mg per day Ethambutol 400mg every 8hours and Isoniazid 300mg per day	Not used	Resolution of BCG[2] disease			

1-TNM: Tumor, Node, Metastasis; 2-BCG: Bacillus Calmette-Guerin; 3- COPD: Chronic obstructive pulmonary disease; 4-CT: computerized tomography; 5- TST: Tuberculin skin test; 6-PCR: Polymerase chain reaction;7- M. Bovis: Mycobacterium bovis

invasive bladder cancer (NMIBC). Its efficacy is well established in decreasing the risk of disease progression and recurrence [13,14].

4.1. BCG immunotherapy's mechanism of action

The mechanism of action of BCG as an immunotherapeutic agent in cancer is not fully known, but evidence suggests that elaboration of cytokines by T helper cells is the key process [6,15]. The most recent evidence supports a BCG induced specific tumor immunity in animal models [16,17].

4.2. Definition of BCG's related severe complications

In one series of Pérez-Jacoiste Asín et al. [10], a systemic adverse event post BCG instillation has been defined as a specific organ infection post BCG instillation responding to antituberculosis treatment with no alternative diagnosis. According to Pommier et al. [11], BCG infection was defined as the occurrence of fever without any other etiology, for at least 48 h, and/or at least one organ involvement other than the bladder, that led to discontinuation of BCG therapy. The diagnosis of an organ involvement was established according to the clinical, biological, and radiological abnormalities [11]. In another review article, systemic complications were defined by the presence of fever, chills, hypotension, and progressive multisystem organ failure [12]. This array of definitions highlights the diversity and complexity of these complications following BCG immunotherapy. The definition used in this study is a mixture of the ones used in other studies: it takes into consideration clinical symptoms and biological examinations. However, this definition uses TST which is non standardized test after BCG treatment.

4.3. Classification of complications of BCG treatment and toxicity differences between several BCG strains

In spite of its importance, BCG immunotherapy may cause some local or systemic side effects and complications [12]. The most important local side effects are irritative urinary symptoms, cystitis and hematuria [8,18]. The most serious complication of intravesical BCG immunotherapy is related to disseminated infection. It can range from infection of an organ to severe sepsis [7,19]. The most frequent systemic adverse events are malaise, fever and lung infection [8,20]. The overall rate of serious complications is estimated to be less than 5% independently of the BCG preparations or doses used [12]. The reported rate of severe complications post intravesical BCG instillation was 1.5% in this study, which is comparable to the one reported in other studies [12]. The majority of side effects occur within the first year of beginning intravesical BCG [8,21].

In this study, the BCG-medac from Germany, RIVM strain was used. The RIVM strain has been associated with more severe, less frequent complications compared to the TICE and Moreau stains [20,22]. Changing the BCG strain during the course of therapy was also associated with more severe toxicity [20]. The complications encountered in the population of this study were severe urinary tract infections and systemic BCG infection involving the bone marrow.

4.4. The cause of the BCG related complications

The exact cause of these BCG related complications remains controversial. Whether due to an hypersensitivity inflammatory reaction [3,23] or an active infection [24], both theories have been widely and profoundly discussed in the literature. In patients four and five, we were able to isolate the M. Bovis's DNA by polymerase chain reaction (PCR) technique which favors more the infection rather than the hypersensitivity theory.

4.5. Tuberculin skin test in BCG infections

Tuberculin skin test (TST) diagnostic technique has seldom been evaluated in the diagnosis of BCG treatment related adverse events. No clear threshold has been established for a positive testing in this setting. The standard ten millimeters limit for positivity was applied in this study to emphasize the high risk that BCG related complications may convey. Patient number 1 had a newly positive TST test, fever and severe irritative urinary symptoms which led to the initiation of an empirical anti-tuberculous therapy with subsequent symptoms clearance and patient survival. A history of BCG vaccine or a positive TST should be taken into consideration before interpreting a new TST in a patient suspected of having a BCG related infection. The TST was used in several studies as an additional argument in the diagnosis of BCG related infections [25,26]. A study comparing TST to interferon-gamma based assay in patients receiving intravesical BCG and exposed to tuberculosis showed that a positive TST was poorly correlated to tuberculosis in BCG patients, and the interferon-gamma based assay was not affected by BCG exposure [27]. Another retrospective study showed that TST was not statistically associated with BCG toxicity [28]. Therefore, more studies are needed to determine the value of TST and interferon-gamma based assay in these populations and careful interpretation of these tests is warranted.

4.6. Risk factors and prevention strategies for BCG related infections

Advanced age, cystitis, immunosuppression and the presence of cracks in the urogenital epithelium prior to treatment are known to be risk factors for the development of disseminated infection [3,10,29]. Patients 1,2,3 and 5 had a traumatic BCG instillation and were aged between 58 and 84 years old.

Several strategies have been tested to try to prevent the BCG related adverse events. Educating the healthcare professional is as important as educating the patient about these side effects. The healthcare professional should master proper catheterization techniques and BCG should not be instilled before a minimum of 2 weeks following a urinary intervention. Four out of five patients in this study had traumatic instillations, which highlights the importance of applying appropriate intravesical instillation techniques. If gross hematuria and/or urinary tract infection are present, then BCG treatment should be deferred until resolution of these symptoms. Whenever a BCG systemic reaction is suspected, early initiation of antitubercular antibiotics is recommended [30]. Screening for urinary infection nor treating asymptomatic bacteriuria prior to BCG treatment decreased the rate of BCG related infections [31,32]. None of our patients had a urinalysis prior to the BCG immunotherapy. Isoniazid prophylaxis around the time of BCG instillation did not decrease the incidence of focal nor systemic complications [33,34]. BCG dose reduction (to one third) did not show a decrease in toxicity compared to the full dose [35]. However, reducing the BCG dwell-time to 30 min could be an alternative to a dose reduction in patients who experience severe side-effects after BCG instillations [36]. Toxicity was reduced when two Ofloxacin doses were given shortly after each BCG instillation (6 h and 18 h after the first urination post instillation) [37]. Prulifloxacin (three capsules of Prulifloxacin 600mg) was also found useful, at least in one study, in decreasing adverse events incidence and improving patients' compliance to therapy [38]. However, no clear recommendation is currently available regarding the use of quinolones to prevent BCG immunotherapy's related adverse events. Traumatic instillation was associated with BCG adverse events in this study. The use of systemic corticosteroids was associated to a worse outcome.

4.7. Treatment strategies for BCG infections

No clear recommendations have been implemented to treat intravesical BCG related adverse events [39]. The recommendations available are based on center experiences and no randomized control trials have been conducted due to the rarity of these complications. Treatment usually varies from antipyretics, nonsteroidal anti-inflammatory drugs to antituberculosis therapy and systemic corticosteroids depending on the extent (local versus systemic) and severity of symptoms [30]. Mycobacterium Bovis, used in BCG instillations, is susceptible to the fluoroquinolones and anti-tuberculosis agents except for Pyrazinamide [40]. Local irritative symptoms should only be treated symptomatically and further BCG instillations should be postponed until resolution of symptoms [41]. Patients on BCG immunotherapy who develop high-grade fever (defined as temperature above 39 °C) should be admitted to hospital for monitoring of signs of BCG sepsis and BCG immunotherapy should be discontinued [42]. The use of anti-tuberculous drugs, whenever combined with corticosteroids or not, is common for both systemic and local forms of BCG infection. Antituberculosis therapy (Rifampin, isoniazid and ethambutol), in conjunction with steroid therapy, should be started empirically while waiting for further investigation results (such as cultures or histology) [42]. Steroids should be tapered gradually after resolution of symptoms otherwise recurrence of symptoms and granuloma formation can be seen [3,23]. The duration of antituberculosis therapy varies from two weeks to six months depending on symptoms severity and infected location [43]. This range of treatment duration is reflected in this study. Patient 2 and 4 received steroids and both had unfavorable outcomes.

4.8. The decision to resume or discontinue the BCG treatment after a related complication

The decision of cessation of further intravesical BCG immunotherapy after a BCG related complication should be discussed on a case by case basis [8]. Complications should be divided into mild to moderate, severe to generalized and immunologic reactions. For mild to moderate reactions, the treatment can be restarted after symptom resolution. For severe or generalized reactions, restarting the instillations should be evaluated according to the risk-benefit ratio with a possible reduction of BCG dosage. For allergic reactions, a close monitoring of the patient during the first hours following instillations should be performed [44].

4.9. Limitations and strengths of the study

This study has several limitations. The data reported is heterogenous and retrospective. No standardized diagnostic tools were used, mainly due to their unavailability in the literature. This study lacks long term complications follow up.

Nonetheless, this study reported five cases of BCG related severe complications, which are rare. No randomized trials, nor prospective studies have been done on this subject because of its rarity and difficulty to diagnose. There are no clear guidelines or recommendations on how to diagnose, manage and treat these BCG related complications.

4.10. New treatment models for NMIBC

Optimization of BCG therapy is under way to improve response to therapy and decrease its side effects and complications. Several ongoing clinical trials are currently in progress to combine BCG therapy for NMIBC with other agent: immuno-modulators, recombinant cytokines or recombinant BCG strains. We are in the middle of a discovery phase of novel immunotherapeutic approaches that may improve BCG therapy and the outcomes for patients with NMIBC [45,46]. Some studies found that having a BCG-specific T-cell immunity before induction of BCG treatment may improve patient outcomes following BCG therapy [47,48], but these results have been contradicted in a recent article [28]. An ongoing trial (NCT03091660) to test this hypothesis and to compare Tokyo-172 BCG and TICE strains in terms of time to high-grade recurrence is underway [49].

Several ongoing trials are being conducted to assess the impact of checkpoint inhibitors in combination with BCG in NMIBC, including the non-responders to the BCG treatment alone (NCT02451423, NCT02625961, NCT02792192, NCT02324582, and NCT02808143) [17]. Immunomodulators combined with BCG therapy are also being studied (NCT03317158, NCT03022825, NCT02015104, NCT02808143, NCT02792192, NCT02324582) [17].

5. Conclusion

Despite its frequent use, BCG immunotherapy's mechanism of action and complications remain controversial. Disseminated BCG infection is a rare, but potentially fatal complication of intravesical BCG therapy for NMIBC. To our knowledge, no standardized or recommended approach is available to readily diagnose such events. Tuberculin skin test evaluation deserves further analysis to better mark its diagnostic implication in these conditions.

Health care professionals must have a high index of suspicion in patients treated with intravesical BCG. A standardized diagnostic and treatment approach should be implemented to help physicians tackle these life-threatening complications.

Optimizing BCG immunotherapies is to be expected in near future, decreasing its side effects and improving its efficacy.

CRediT authorship contribution statement

R. Waked: Writing - original draft. **J. Choucair:** Writing - original draft. **N. Chehata:** Supervision, Writing - review & editing. **E. Haddad:** Writing - original draft. **G. Saliba:** Conceptualization, Validation.

Declaration of Competing Interest

None.

Acknowledgments

Not applicable.

Ethics approval and consent to participate

Authorization by the ethical committee of the Saint Joseph University, Beirut, Lebanon for data processing and publication was obtained (number CEHDF 1352).

Consent for publication

Written informed consent was obtained from the patient or the next of kin for publication of this article.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

No special funds were used for this study.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359–86.
[2] Unda-Urzaiz M, Cozar-Olmos JM, Miñana-Lopez B, Camarero-Jimenez J, Brugarolas-Rossello X, Zubiaur-Libano C, et al. Safety and efficacy of various strains of Bacille Calmette–Guérin in the treatment of bladder tumors in standard clinical practice. Actas Urol Esp Engl Ed 2018;42(4):238–48.
[3] Elkabani M, Greene JN, Vincent AL, Vanhook S, Sandin RL. Disseminated mycobacterium bovis after intravesicular Bacillus Calmette-Guérin treatments for bladder cancer. Cancer Control 2000;7(5):476–81.
[4] Han RF, Pan JG. Can intravesical Bacillus Calmette-Guérin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. Urology 2006;67(6):1216–23.
[5] Shelley MD, Mason MD, Kynaston H. Intravesical therapy for superficial bladder cancer: a systematic review of randomised trials and meta-analyses. Cancer Treat Rev 2010;36(3):195–205.
[6] Mungan W. Bacille Calmette-Guérin in superficial transitional cell carcinoma. Br J Urol. 1998;82(2):213–23.
[7] Liu Y, Lu J, Huang Y, Ma L. Clinical spectrum of complications induced by intravesical immunotherapy of Bacillus Calmette-Guérin for bladder cancer. J Oncol 2019 [cited 2019 Jun 14]2019. Available from. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6431507/.
[8] Brausi M, Oddens J, Sylvester R, Bono A, van de Beek C, van Andel G, et al. Side effects of Bacillus Calmette-Guérin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. Eur Urol 2014;65(1):69–76.
[9] Kamat AM, Bellmunt J, Galsky MD, Konety BR, Lamm DL, Langham D, et al. Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma. J Immunother Cancer 2017;5 [cited 2019 Jun 15]Available from. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5557323/.
[10] Pérez-Jacoiste Asín MA, Fernández-Ruiz M, López-Medrano F, Lumbreras C, Tejido Á, San Juan R, et al. Bacillus Calmette-Guérin (BCG) infection following intravesical bcg administration as adjunctive therapy for bladder cancer. Medicine 2014;93(17) [cited 2019 Jun 16]Available from. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4602419/.
[11] Pommier JD, Lasfar NB, Grunderbeeck NV, Burdet C, Laouénan C, Rioux C, et al. Complications following intravesical Bacillus Calmette-Guerin treatment for bladder cancer: a case series of 22 patients. Infect Dis 2015;47(10):725–31.
[12] Lamm DL. Efficacy and safety of Bacille Calmette-Guérin immunotherapy in superficial bladder cancer. Clin Infect Dis 2000;31(Supplement_3):S8–90.
[13] Sylvester RJ, van der MEIJDEN APM, Lamm DL. Intravesical Bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol. 2002;168(5):1964–70.
[14] Serretta V, Gesolfo CS, Alonge V, Cicero G, Moschini M, Colombo R. Does the compliance to intravesical BCG differ between common clinical practice and international multicentric trials? Urol. Int. 2016;96(1):20–4.
[15] Mitropoulos DN. Novel insights into the mechanism of action of intravesical immunomodulators. In Vivo 2005;19(3):611–21.
[16] Vandeveer AJ, Fallon JK, Tighe R, Sabzevari H, Schlom J, Greiner JW. Systemic immunotherapy of non-muscle invasive mouse bladder cancer with avelumab, an anti-PD-L1 immune checkpoint inhibitor. Cancer Immunol Res 2016;4(5):452–62.
[17] Pasteur research pasteur fr-Institut. Building on a solid foundation: enhancing Bacillus Calmette-Guérin therapy | research – institut pasteur [Internet]. [cited 2020 Jan 26]. Available from: https://research.pasteur.fr/en/publication/building-on-a-solid-foundation-enhancing-bacillus-calmette-guerin-therapy/.
[18] Shelley M, Court JB, Kynaston H, Wilt TJ, Fish R, Mason M. Intravesical Bacillus Calmette-Guérin in Ta and T1 bladder cancer. Cochrane Database Syst Rev 2000(4) [cited 2019 Jun 16]Available from. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001986/full.
[19] Gonzalez OY, Musher DM, Brar I, Furgeson S, Boktour MR, Septimus EJ, et al. Spectrum of Bacille Calmette-Guérin (BCG) infection after intravesical BCG immunotherapy. Clin Infect Dis 2003;36(2):140–8.
[20] Krajewski W, Matuszewski M, Poletajew S, Grzegrzółka J, Zdrojowy R, Kołodziej A. Are there differences in toxicity and efficacy between various Bacillus Calmette–Guerin strains in bladder cancer patients? Analysis of 844 patients. Urol Int 2018;101(3):277–84.
[21] van der Meijden APM, Sylvester RJ, Oosterlinck W, Hoeltl W, Bono AV. Maintenance Bacillus Calmette-Guerin for Ta T1 bladder tumors is not associated with increased toxicity: results from a european organisation for research and treatment of cancer genito-urinary group phase III trial. Eur Urol 2003;44(4):429–34.
[22] Farah NB, Ghanem R, Amr M. Treatment efficacy and tolerability of intravesical Bacillus Calmette-Guerin (BCG) – RIVM strain: induction and maintenance protocol in high grade and recurrent low grade non-muscle invasive bladder cancer (NMIBC). BMC Urol 2014;14:11.
[23] Barza MJ, Blum JH, Graeme-Cook FM. Case 29-1998. N Engl J Med 1998;339(12):831–7.
[24] Wolf YG, Wolf DG, Higginbottom PA, Dilley RB. Infection of a ruptured aortic aneurysm and an aortic graft with Bacille Calmette-Guérin after intravesical administration for bladder cancer. J Vasc Surg 1995;22(1):80–4.
[25] Michałowska-Mitczuk D, Brzezińska S, Augustynowicz-Kopeć E, Langfort R. Granuloma of epididymis of patient treated with intravesical BCG therapy — complication of BCG therapy or tuberculosis? Adv Respir Med. 2011;79(4):305–8.
[26] Numao N, Goto S, Suzuki S. A case of renal tuberculosis following bacillus Calmette-Guerin instillation therapy for bladder cancer. Hinyokika Kiyo 2000;46(2):109–11.
[27] Silverman MS, Reynolds D, Kavsak PA, Garay J, Daly A, Davis I. Use of an interferon-gamma based assay to assess bladder cancer patients treated with intravesical BCG and exposed to tuberculosis. Clin Biochem 2007;40(12):913–5.
[28] Krajewski W, Zdrojowy R, Grzegółka J, Krajewski P, Wróbel M, Luczak M, et al. Does mantoux test result predicts BCG immunotherapy efficiency and severe toxicity in non-muscle invasive bladder cancer. Urol J 2019;16(5):458–62.

[29] Heiner JG, Terris MK. Effect of advanced age on the development of complications from intravesical bacillus Calmette-Guérin therapy. Urol Oncol Semin Orig Investig 2008;26(2):137–40.
[30] Witjes JA, Palou J, Soloway M, Lamm D, Brausi M, Spermon JR, et al. Clinical practice recommendations for the prevention and management of intravesical therapy – associated adverse events. Eur Urol Suppl 2008;7(10):667–74.
[31] Zhao LC, Meeks JJ, Helfand BT, Ross FR, Herr HW, Kundu SD. Screening urine analysis before Bacille Calmette-Guérin instillation does not reduce the rate of infectious complications. BJU Int 2012;109(12):1819–21.
[32] Herr HW. Outpatient urological procedures in antibiotic-naive patients with bladder cancer with asymptomatic bacteriuria. BJU Int 2012;110(11b):E658–60.
[33] Vegt PDJ, van der Meijden APM, Sylvester R, Brausi M, Holtl W, de Balincourt C. Does isoniazid reduce side effects of intravesical Bacillus Calmette-Guerin Therapy in superficial bladder cancer? Interim results of european organization for research and treatment of cancer protocol 30911. J Urol 1997;157(4):1246–9.
[34] Van der meijden APM, Brausi M, Zambon V, Kirkels W, De balincourt C, Sylvester R. Intravesical instillation of epirubicin, Bacillus Calmette-Guerin and Bacillus Calmette-Guerin plus isoniazid for intermediate and high risk Ta, T1 papillary carcinoma of the bladder: a European organization for research and treatment of cancer genito-urinary group randomized phase iii trial. J Urol. 2001;166(2):476–81.
[35] Oddens J, Brausi M, Sylvester R, Bono A, van de Beek C, van Andel G, et al. Final results of an EORTC-GU cancers group randomized study of maintenance Bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol 2013;63(3):462–72.
[36] Andius P, Fehrling M, Holmäng S. Intravesical bacillus Calmette-Guèrin therapy: experience with a reduced dwell-time in patients with pronounced side-effects. BJU Int 2005;96(9):1290–3.
[37] Marc Colombel, Fabien Saint, Dominique Chopin, Bernard Malavaud, Ludovic Nicolas, Pascal Rischmann, et al. The effect of ofloxacin on Bacillus Calmette-Guerin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study. J Urol 2006;176(3):935–9.
[38] Damiano R, Sio MD, Quarto G, Lorenzo GD, Perdonà S, Palumbo IM, et al. Short-term administration of prulifloxacin in patients with nonmuscle-invasive bladder cancer: an effective option for the prevention of bacillus Calmette-Guérin-induced toxicity? BJU Int 2009;104(5):633–9.
[39] Malhotra P, Farber BF. Isoniazid resistance among Bacillus Calmette Guerin strains: implications on bladder cancer immunotherapy related infections. Can J Urol 2011;18(3):5671–5.
[40] Durek C, Rüsch-Gerdes S, Jocham D, Böhle A. Sensitivity of BCG to modern antibiotics. Eur Urol 2000;37(Suppl. 1):21–5.
[41] Lamm DL, Van Der Meijden APM, Morales A, Brosman SA, Catalona WJ, Herr HW, et al. Incidence and treatment of complications of Bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol 1992;147(3, Part 1):596–600.
[42] Huang T.C.Management of Complications of Bacillus Calmette-Guérin Immunotherapy in the Treatment of Bladder Cancer.:4.
[43] Lamm DL. Complications of Bacillus Calmette-Guérin immunotherapy. Urol Clin North Am 1992;19(3):565–72.
[44] Rischmann P, Desgrandchamps F, Malavaud B, Chopin DK. BCG intravesical instillations: recommendations for side-effects management. Eur Urol 2000;37(Suppl 1):33–6.
[45] Building on a Solid Foundation: Enhancing Bacillus Calmette-Guérin Therapy – ClinicalKey [Internet]. [cited 2019 Jun 20]. Available from: https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S2405456918303110?returnurl=null&referrer=null&scrollTo=%23hl0000341.
[46] Dovedi SJ, Kirby JA, Davies BR, Leung H, Kelly JD. Celecoxib has potent antitumour effects as a single agent and in combination with BCG immunotherapy in a model of urothelial cell carcinoma. Eur Urol 2008;54(3):621–30.
[47] Niwa N, Kikuchi E, Matsumoto K, Kosaka T, Mizuno R, Oya M. Purified protein derivative skin test reactions are associated with clinical outcomes of patients with nonmuscle invasive bladder cancer treated with induction bacillus Calmette-Guérin therapy. Urol Oncol Semin Orig Investig 2018;36(2):77.e15–21.
[48] Werner Luftenegger, Ackermann Daniel K, Futterlieb Andrea, Kraft Rainer, Minder Christoph E, Nadelhaft Peter, et al. Intravesical versus intravesical plus intradermal Bacillus Calmette-Guerin: a prospective randomized study in patient with recurrent superficial bladder tumors. J Urol 1996;155(2):483–7.
[49] Svatek RS, Tangen C, Delacroix S, Lowrance W, Lerner SP. Background and update for S1602 “a phase III randomized trial to evaluate the influence of BCG strain differences and T cell priming with intradermal BCG before intravesical therapy for BCG-naïve high-grade non-muscle-invasive bladder cancer. Eur Urol Focus 2018;4(4):522–4.