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Safety and Efficacy of Intravesical Bacillus Calmette-Guérin Immunotherapy in Patients with Non-Muscle-Invasive Bladder Cancer Presenting with Asymptomatic Bacteriuria: A Systematic Review

Keywords

Bacillus Calmette-Guérin · Bacteriuria · Bladder cancer · Intravesical instillation

Abstract

Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy in bladder cancer patients with asymptomatic bacteriuria (ABU) remains a matter of debate. The aim of this systematic review was to present available evidence on the safety and efficacy of BCG immunotherapy in patients with ABU. A literature search within the Medline and the Embase databases was conducted with the following search terms: adverse events, bacteriuria, BCG, bladder cancer, cystitis, infection, pyuria, side effects and urinary tract infection (UTI). Sixteen relevant original articles were identified, including 6 articles directly presenting the safety or efficacy of BCG therapy in patients with ABU. None of them was a randomized controlled trial. Intravesical BCG instillations in patients with ABU were not associated with the increased risk of symptomatic UTI and did not affect negatively the recurrence- or progression-free survival. Routine urine analysis before BCG instillation created increased cost and potentially unnecessary delays in BCG therapy. ABU does not affect negatively the safety and efficacy of intravesical BCG

immunotherapy. There is no evidence to support routine screening and treatment of ABU in patients scheduled for intravesical BCG instillations due to bladder cancer. However, this issue was not addressed adequately and needs further research.

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Introduction

Adjuvant intravesical immunotherapy with Bacillus Calmette-Guérin (BCG) is a standard treatment in patients with high-risk, non-muscle-invasive bladder cancer after the surgery. It reduces the risk of disease recurrence, delays progression and improves overall survival [1, 2]. However, the therapy is associated with significant risk of local and systemic adverse events [3]. As the urinary tract infection (UTI) is regarded a risk factor of BCG complications, symptomatic UTI is an absolute contraindication to the therapy [1].

Although widely accepted, the association between UTI and the safety of BCG therapy was poorly studied and the evidence in this field is limited. Simultaneously, many urologists consider sterile urine as a sine-qua-non condition for intravesical BCG instillation [4]. Some ex-

Fig. 1. The flow of information through the different phases of the systematic review (adopted from www.prisma-statement.org).

Color version available online

perts believe that bacterial cystitis causes traumatization of the barrier for the BCG to reach the bloodstream [5]. However, the antimicrobial treatment delays adjuvant oncological treatment and potentially contributes to the increase in bacterial resistance to antibiotics, while the clinical benefit is not clear. Clinical safety and efficacy of the treatment are particularly interesting to observe in patients with asymptomatic bacteriuria (ABU), a common condition in male patients in their sixth and seventh decades of life. A majority of them have benign prostate hyperplasia and urinary retention; all of them undergo transurethral procedures for bladder cancer (cystoscopy, resection). Consequently, they have at least few important risk factors of bacteriuria, which is reported in 28–54% of patients with benign prostate hyperplasia, 17% of patients undergoing cystoscopy and 2–39% of patients after the transurethral resection of the bladder tumour [6–8]. Simultaneously, positive urine culture in otherwise asymptomatic patients seems to be one of the most common reasons for the delay of the BCG immunotherapy, what – in turn – probably reduces the clinical efficacy of the treatment [9].

The aim of this systematic review was to present available evidence regarding the safety and efficacy of intravesical BCG instillations in patients with ABU.

Evidence Acquisition

To address the aim of this review, authors asked the following 4 clinical questions:

1. Does ABU increase the risk of febrile UTI or other complications in patients undergoing BCG intravesical instillations?
2. Does ABU affect the efficacy of BCG intravesical instillations?
3. Is it justified to screen asymptomatic patients for bacteriuria before BCG therapy?
4. Is it possible to reduce the risk of UTI related to BCG intravesical instillation?

A literature search within the Medline and the Embase databases was conducted in December 2016 for papers presenting the safety or efficacy of intravesical BCG immunotherapy in patients with ABU. The following search terms were used: adverse events, BCG, bacteriuria, bladder cancer, cystitis, infection, pyuria, side effects and UTI. The search was limited to publications in English, French and Spanish with no additional filters.

Sixteen relevant original articles were identified (Fig. 1). Full texts of all of them were retrieved. Among them, 6 articles related directly to the relationship between ABU and the safety or efficacy of BCG therapy; 3 discussed py-

Table 1. The overview of available evidence on the risk of febrile UTI in patients undergoing intravesical BCG instillations with ABU and sterile urine

Author, year	Number of patients	Percentage of patients with ABU, %	Follow-up, months	Rate of febrile UTI, %	<i>p</i> value
Herr [10], 2011	200	25	3	1.9 vs. 0.6	ns
Herr [6], 2012	440	30	1	0.8 vs. 3.6	0.001
Herr [11], 2012	243	25	12 (<i>n</i> = 243) 24 (<i>n</i> = 156)	1.6 vs. 0.5	ns
Herr [12], 2016	354	25	3	1.1 vs. 2.2	ns

BCG, Bacillus Calmette-Guérin; ABU, asymptomatic bacteriuria; UTI, urinary tract infection.

Table 2. The overview of available evidence on the survival of patients undergoing intravesical BCG instillations with ABU and sterile urine

Author, year	Number of patients	Percentage of patients with ABU, %	BCG strain	Follow-up, months	Recurrence rate, %	<i>p</i> value	Progression rate, %	<i>p</i> value
Herr [11], 2012	243	25	Connaught	12 (<i>n</i> = 243) 24 (<i>n</i> = 156)	27 vs. 29	ns	6.5 vs. 13	ns
Herr and Donat [15], 2016	459	31	Not specified	24	18 vs. 28	0.03	8 vs. 11	ns

BCG, Bacillus Calmette-Guérin; ABU, asymptomatic bacteriuria; UTI, urinary tract infection.

uria as a prognostic factor, 1 was focused on the response to BCG and 6 presented side effects of BCG therapy and their management.

Evidence Synthesis

Does ABU Increase the Risk of Febrile UTI or Other Complications in Patients Undergoing BCG Intravesical Instillations?

The observational studies published by Herr [6, 10–12] assessed the safety of BCG intravesical instillations in patients with ABU. The results of these studies are presented in Table 1. The risk of febrile UTI did not differ between patients with ABU and sterile urine in 2 studies and surprisingly favoured ABU in one study. Lower risk of UTI in patients with ABU was subsequently explained by the intense immune response to intravesical BCG instillations and its antimicrobial activity. In another study by Herr [13], among patients with bladder cancer and ABU, who did not receive antibiotics, positive urine culture during the follow-up was 2.4-fold less likely when BCG therapy was applied. In all cases of febrile UTI, symptoms resolved with culture-directed antibiotics and only 1 patient from all 4 reports required hospitalization.

Contrary to the above-mentioned studies, Perez-Jacoiste Asin et al. [14] noticed that systemic complications of BCG therapy were more likely in patients who underwent manipulations within the lower urinary tract, including transurethral fulguration, intravesical chemotherapy instillation, or radiotherapy. As all these interventions share with bacteriuria the disruption of bladder mucosa, one can suggest that ABU would also increase the risk of systemic complications. However, this was not tested within the study.

Does ABU Affect the Efficacy of BCG Intravesical Instillations?

Table 2 presents the results of observational studies assessing the efficacy of BCG intravesical instillations in patients with ABU. Both these studies showed that ABU does not increase the risk of bladder cancer recurrence and progression, while one study presented a lower recurrence rate and longer time to recurrence in patients with ABU than in patients with sterile urine [11, 15]. This phenomenon could be potentially explained by the intense immunological response, triggered not only by BCG, but also by ABU [15]. Finally, leukocytes, recruited and mi-

grated into the bladder during the immunological response to BCG [16], were postulated to predict the recurrence-free survival [17, 18]. However, the URO-BCG-4 study did not confirm these findings [19].

Is It Justified to Screen Asymptomatic Patients for Bacteriuria before BCG Therapy?

The rationale for routine screening for bacteriuria in asymptomatic patients undergoing BCG intravesical instillations was addressed by Zhao et al. [20] in a retrospective analysis. They found that the risk of UTI is equal in patients who are screened and who are not screened for ABU and reaches 3% in both groups after BCG instillations. The urine culture was positive in 18% of cases in the screening group and its positive predictive value for UTI was 0.9%. Moreover, BCG therapy was delayed in 2.5% of patients from the screening group due to additional treatment. Authors concluded that routine urine analysis before BCG instillation creates increased cost, potentially unnecessary delays in BCG therapy and can safely be omitted in asymptomatic patients.

Is It Possible to Reduce the Risk of UTI Related to BCG Intravesical Instillation?

It was postulated that the risk of UTI related to BCG instillation could be decreased with the use of fluoroquinolones after the intravesical instillation. In the prospective randomized controlled trial published by Colombel et al. [21], 2 doses of ofloxacin decreased the rate of moderate and severe adverse events by 18.5%, both local and systemic. Similar findings for 3 doses of prulifloxacin were reported by Damiano et al. [22] in another randomized controlled trial. Unfortunately, none of the studies presented detailed data on the incidence of UTI, while the rate of dysuria after BCG instillations was similar in patients receiving and not receiving antibiotics. On the contrary, the EORTC study did not find any benefit in the prophylactic use of isoniazid at the time of BCG instillation in terms of the risk of bacterial cystitis [23]. Finally, the optimal timing of possible antibiotic administration also remains unclear, although it probably should be delayed to avoid the possible inhibition of antitumor efficacy by the eradication of living BCG organisms [24].

Discussion

We present a short review of the available literature in the field of intravesical BCG immunotherapy in patients with bacteriuria. Existing evidence suggest that there is no

need for routine urine culture in asymptomatic patients, as BCG instillations in patients with ABU are as safe and effective as in patients with sterile urine. Moreover, antibacterial properties of intravesical BCG installations were proposed.

The main limitations of clinical conclusions are the low number and the observational character of almost all available studies, as well as the fact that a majority of the studies were conducted by the same researcher. This means they are all single-institution studies based on the experience of a single surgeon. Moreover, these articles come from one high-volume tertiary centre, where the patients were treated by an extremely experienced urologist. Interestingly, in the studies involving patients with ABU, the overall rate of febrile UTI after BCG instillations was very low, potentially leading to the underpowered results. In the historical study concerning the adverse events of BCG instillations during the maintenance therapy, van der Meijden et al. [25] noticed bacterial cystitis in 26% of patients during the follow-up with weekly urine culture. More recently, Brausi et al. [3] in the EORTC study noticed bacterial cystitis in 23% of patients receiving maintenance BCG therapy. Finally, the criterion of febrile UTI and positive urine culture was the end point in all the studies, while nonfebrile UTIs were not considered.

Conclusions

ABU does not increase the risk of infective complications of BCG intravesical instillations and does not affect negatively the efficacy of BCG therapy. By consequence, available evidence does not support the need for routine screening and treatment of ABU in patients with bladder cancer who are scheduled for intravesical BCG instillations. However, this issue is not addressed adequately and needs further research, including dedicated randomized controlled trials. Symptomatic UTI remains an absolute contraindication for BCG therapy.

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