Mini Review

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Intravesical Bacillus Calmette-Guérin Treatment During The Coronavirus Disease-2019 Pandemic: A Review of Current Recommendations

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Abstract

Objective: Many outpatient procedures were restricted to reduce the likelihood of transmission during the coronavirus disease-2019 (COVID-19) pandemic. The most effective treatment of high-risk non-muscle-invasive bladder cancer (NMIBC) is the intravesical Bacillus Calmette-Guérin (BCG) therapy, consisting of induction and maintenance, which requires repeated hospital visits. Therefore, treatment protocol adaptation to the pandemic is important.

Materials and Methods: A comprehensive literature review was performed between January 2020 and December 2020 within the PubMed and Google Scholar databases.

Results: Recommendations and updates of two international associations, two national associations, and five intravesical BCG application studies were discussed. During the pandemic, intravesical BCG treatment was delayed for patients with NMIBC in the intermediate-risk group. The general view for patients in the high-risk group is to complete induction therapy, if possible. Recommendations for maintenance treatment vary. With this treatment, planning should be done in less than one year. The existence of suspected or approved COVID-19 disease delayed the BCG treatment for 3 weeks.

Conclusion: Consensus was not found on how intravesical BCG treatment should be applied during the pandemic. However, it is recommended to at least complete induction therapy in high-risk NMIBC as the risk of progression and recurrence is high. BCG instillations can be delayed for at least 3 weeks in patients with confirmed COVID-19 disease.

Keywords: Bladder cancer, intravesical BCG, COVID-19, coronavirus, pandemic

Introduction

In the second half of 2019, new cases of pneumonia emerged in Wuhan, China, and the World Health Organization named this coronavirus disease-2019 (COVID-19) and shortly thereafter declared it a pandemic (1). Clinicians adjusted all their clinical practices, especially life-threatening malignant disorders, to address the COVID-19 pandemic. One such practice involved intravesical Bacillus Calmette-Guérin (BCG) treatment, which is the gold standard method in high-risk non-muscle-invasive bladder cancer (NMIBC). This treatment reduces recurrence rates for NMIBC by 60%-70% and progression by 26% (2). However, it requires repeated hospital admissions, which increase the risk of contamination during the pandemic, thus rearranging the treatment algorithm in this patient group is necessary (3). National and international urological associations (4,5,6,7) have outlined internationally recognized standards of care and published guidelines and recommendations in triaging patients throughout the COVID-19 outbreak. This report aimed to present the guidelines and recommendations updates in the literature regarding intravesical BCG administration during the COVID-19 outbreak.

Materials and Methods

The recommendations and updates published by the national and international urology associations in intravesical BCG treatment application during the pandemic were screened in this literature review.

A comprehensive search of PubMed and Google Scholar was undertaken from January through December 2020 to find available published works in triaging patients with bladder cancer who are candidates for intravesical BCG therapy during the pandemic. The search items used were "coronavirus," "COVID-19," "pandemic," "SARS-CoV-2," "bladder cancer," "urothelial carcinoma," "Bacillus Calmette-Guérin," "intravesical

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BCG," "treatment," "guidelines," and "recommendations." Original articles, review articles, commentaries, editorials, letters to editors, and research letters were included. Non-English publications and studies on COVID-19 that were outside the scope of our research were excluded.

Therefore, nine publications formed the basis of our review article, wherein two were from the international urology associations, two from the national urology associations, and five from urology experts.

Results

Recommendations of International Urological Associations

The team at the European Association of Urology guidelines department was quick to respond and made recommendations according to the priority levels for various situations that were affected by the pandemic. Intravesical BCG therapy for intermediate-risk NMIBC was given a low priority due to unexpected clinical damage (progression/metastasis) unless the treatment is delayed for >6 months. However, high-grade NMIBC is a high priority, and intravesical BCG instillations should be started within 6 weeks (4).

Some theories suggest that BCG vaccination protects against COVID-19 disease. BCG vaccines showed protection against some DNA and RNA viruses by working on the innate immune system and producing memory-like responses (8,9). Indeed, by the first half of 2020, the lack of a specific COVID-19 vaccine leads to a possible BCG shortage. The American Urological Association also made its recommendations for intravesical BCG application based on the possibility of global BCG shortage. Patients who are at high risk should be given priority for full induction BCG therapy, and with favorable conditions, the dose could be reduced by 1/2 to 1/3 in these patients. Patients with planned maintenance treatment should be given 1/3 BCG doses, limited to one year (5).

National Urological Association Recommendations

The guideline of the British Association of Urological Surgeons (BAUS) (6) regarding intravesical treatment administrations throughout the COVID-19 pandemic was first announced on March 19, 2020. The first version of the BAUS guideline was recommended against intravesical instillations (BCG or chemotherapy) for NMIBC due to possible immunosuppressive effects. A completed induction course is recommended if intravesical BCG therapy is initiated, with delayed maintenance therapy. BAUS published a second version of the guidelines on March 31, 2020, with an update for NMIBC recommending that the risk/benefit ratio of giving or maintaining intravesical instillation (BCG or chemotherapy) be considered.

The Turkish Uro-oncology Association (TUOA) does not recommend delaying intravesical BCG treatment with suitable current conditions of the institution, as the risk of disease progression is high. However, the TUOA suggests that intravesical therapy in patients with low-to-moderate risk NMIBC can be delayed during the COVID-19 pandemic (7).

Expert Opinions and Literature Recommendations

Cases of high-grade NMIBC benefit the most from induction and initial maintenance BCG doses (so-called 6+3) (10). Therefore, Wallis et al. (11) recommend this as the first line of treatment. The decision about BCG therapy initiation immediately following resection depends on the risk of infection with severe acute respiratory syndrome coronavirus 2 and the adverse course of COVID-19, risk of bladder tumors, and available health care capacity. BCG maintenance is not performed after the first 3-month booster series until the risks of COVID-19 are reduced.

A representative collection of urologists from various institutions in the United States with expertise in different sub-specialties of urology also made separate comments and recommendations regarding the induction and maintenance of intravesical BCG during the pandemic. Induction intravesical BCG treatment provides a significant benefit by reducing the disease recurrence and progression in patients with high-risk or intermediate NMIBC, thus prioritized treatment application is recommended. Maintenance therapy is essential; however, maintenance therapy should be stopped during the pandemic since the most significant intravesical therapy benefits are seen during the induction. Its usage and necessity should be reevaluated within 3 months of the induction course (12).

Panels of Italian and U.S. experts (13,14) recommended intravesical BCG therapy continuation throughout the COVID-19 outbreak, as it is the gold standard adjuvant therapy for recurrence and progression prevention in patients with high-risk NMIBC (2). U.S. experts suggested that after the completion of the first four doses of induction therapy, the remaining doses are administered after a few weeks. Treatment application in a healthcare facility poses a higher risk of getting the virus than the risk involved in postponing 5-6 doses for several weeks. However, if the patient is on the third dose of induction therapy, the fourth dose should be given even if the fifth and sixth doses are delayed. The first and second doses can be taken and the third dose can be skipped entirely in maintenance BCG treatment (14).

Current Recommendations for Patients Diagnosed with COVID-19 During Intravesical BCG Treatment

Recommendations were generally related to intravesical BCG treatment application during the pandemic. However, the specific direction was not reported for patients diagnosed with COVID-19 while receiving intravesical BCG therapy. Lenfant et al. (3) suggested that for induction BCG, BCG instillations can be delayed for at least 3 weeks after initial symptoms to allow complete recovery if the patient has COVID-19 disease. For maintenance BCG, patients with intravesical BCG therapy for >1 year can safely terminate this therapy. However, two of the three doses of the maintenance BCG course may be accepted in maintenance treatment <1 year, and treatment should be delayed for 3 weeks if confirmed with COVID-19 disease.

As summarized in Table 1, a consensus was not made on how intravesical BCG treatment should be applied during the

Table 1. Recommendations on intravesical BCG application during the COVID-19 pandemic	
	Recommendations
EAU (4)	High-risk NMIBC is a high priority, should start in 6 weeks Intermediate-risk NMIBC is a low priority, can delay 6 months
AUA (5)	Induction: High-risk patients full dose, if favorable 1/2 or 1/3 dose BCG shortage possibility Maintenance: 1/3 dose BCG limited in 1 year
BAUS (6)	Induction: Should be completed if possible Maintenance: Based on risk/benefit
TUOA (7)	High-risk NMIBC: postponement is not recommended Intermediate-risk NMIBC: can be postponed
Wallis et al. (11)	High-grade NMIBC: Induction and first maintenance BCG (6 + 3) should be given, other maintenance doses may not be given
Katz et al. (12)	Induction: These patients should be prioritized for treatment, though they may also require a delay in therapy depending on local needs/resources Maintenance: Stop maintenance therapy and re-evaluate its usage/necessity in 3 months
Ficarra et al. (13)	Intermediate-risk NMIBC: postpone High-risk NMIBC: do not postpone
BCAN (14)	Induction: The first four doses may be sufficient Maintenance: Take the first and second doses and skip the third dose
Lenfant et al. (3)	Induction: If COVID-19 positive, 3 weeks delay If COVID-19 negative, 1 weekly instillation for 6 weeks Maintenance: Ongoing maintenance <1 year, 2 out of 3 doses (3 weeks delay if COVID-19 positive) Ongoing maintenance >1 year, safely terminated
EAU: European Association of Urology, AUA: American Urological Association, BAUS: British Association of Urological Surgeons, TUOA: Turkish Uro-oncology Association, BCAN: Bladder Cancer Advocacy Network	

pandemic process. However, some critical points stand out. Intravesical BCG treatment was not proven to poses an infection risk during the COVID-19 pandemic; however, this treatment can be delayed in the intermediate-risk group. The general recommendation is complete induction therapy for patients with high-risk NMIBC, if possible.

Conclusion

Intravesical BCG applications during the pandemic may increase the risk of viral contamination for both the patient and the healthcare staff. However, disruption or delay of this treatment may cause bladder cancer recurrence and progression, especially in high-risk patients. Therefore, intravesical BCG treatment adaptation to the pandemic is essential. Induction therapy should be given, especially in patients with high-risk NMIBC. Maintenance treatment administration should not exceed one year. Treatment should be delayed for 3 weeks in patients diagnosed with COVID-19.

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