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Mini Review

Intravesical BCG amid COVID-19: To give or not to give?

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ABSTRACT

During the coronavirus disease 2019 pandemic, there has been a reduction in the provision of all elective services. This poses enormous pressure on urologists as regards to patients with bladder cancer who need intravesical Bacille Calmette Guerin (BCG) treatment. The evolving situation of the pandemic mandates a pragmatic approach in clinical decisions; to date, there are no uniform consensus guidelines about how to manage these patients and the factors affecting our decision for service provision. These concerns need to be addressed not only for the current crisis but also for the upcoming next phase of the pandemic.

Keywords: Bladder cancer; Bacille Calmette Guerin (BCG); coronavirus disease 2019; pandemic; urology.

Introduction

Coronavirus disease 2019 (COVID-19) pandemic is overwhelming for all healthcare systems.[1] The need to reduce the elective service provision created an atmosphere of uncertainty about what to do and what not to do. Given this unprecedented situation, there is no clear map to how to manage patients.

High grade non-muscle invasive bladder cancer (NMIBC) represents a significant sector of our daily practice with patients. Intravesical Bacille Calmette Guerin (BCG) remains the gold-standard adjuvant treatment for these patients to prevent recurrence and progression.[2] Given the currently evolving situation with COVID-19 pandemic, there are concerns regarding whether to continue giving BCG adjuvant treatment and about how to proceed, given the current limitations in service provision.

Induction BCG instillations are given according to six weekly schedules introduced originally by Morales et al.[2,3] On the other hand, many different maintenance schedules have been used ranging from a total of 10 instillations given in 18 weeks to 27 instillations over 3 years. The European Organization for Research and Treatment of Cancer meta-analysis was not conclusive regarding which schedule was the most effective, but Bohle et al. concluded that at least 1 year of maintenance BCG is required to obtain superiority of BCG over Mitomycin C for the prevention of recurrence and progression.[2,3]

Accordingly, a patient who completed 1 year of maintenance BCG treatment can be discharged given the current pandemic situation.

National and international urological societies[4,5] are publishing some guidelines to help urologists in making judicious clinical decisions through this challenging time. This reduction in service provision may deviate us from the internationally accepted standard of care during the current COVID-19 pandemic.

The British Association of Urological Surgeons (BAUS) published the following COVID-19 policy for bladder cancer management[4]:

- Initially, version 1, released on March 19, 2020, stated "No role for intravesical instillation (BCG or chemotherapy) for non-muscle invasive bladder cancer due to potential immunosuppressive effects."
- This recommendation changed in version 2, released on March 31, 2020, into "Consider the risk/benefit ratio of giving or continuing intravesical instillations (BCG or chemo-

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therapy) for non-muscle invasive bladder cancer, due to their potential immunosuppressive effects."

- BAUS COVID-19 policy for patients already on intravesical chemotherapy/BCG: complete induction if possible and then deferring further treatment.

Recently, European Association of Urology COVID-19 guidelines, published on April 17, 2020, recommended that intravesical BCG treatment for intermediate risk NMIBC is given a low priority because clinical harm (progression/metastasis) is very unlikely if postponed by 6 months. Meanwhile, high grade NMIBC is a high priority, and adjuvant BCG treatment needs to be started within 6 weeks of transurethral resection of bladder tumor.[6]

As suggested by a panel of experts in the USA, intravesical BCG should be continued during the COVID-19 pandemic because, to date, there are no reports that patients receiving intravesical BCG have a higher risk of contracting COVID-19.[7]

For induction therapy, it is suggested that if a patient has had four doses, it is possible to wait a few weeks before receiving the remaining doses. The risk of contracting the virus when coming to a healthcare facility for this treatment is higher than any risk of delaying doses five and six for several weeks. If a patient is still on the third dose, the fourth dose should be given before delaying the remaining treatments. If patients are on maintenance therapy, receiving doses one and two and skipping dose three completely is acceptable.[8,9]

A more recent publication suggested a simple algorithm for BCG instillation for high risk NMIBC, taking into consideration the COVID-19 status of the patient. For induction BCG, if the patient is positive for COVID-19, the induction course can be delayed for 3 weeks. For maintenance BCG, if the patient has completed 1 year of maintenance, then the maintenance course can be safely terminated. If the patient has completed less than 1 year of maintenance BCG, 2 of 3 doses are enough with 3 weeks delay in starting the maintenance, if positive for COVID-19.[10]

Main Points:

- Intravesical Bacille Calmette Guerin (BCG) service provision has been a subject of debate amid COVID-19 crisis; to date, there is no standardized protocol about how to provide this adjuvant treatment during the pandemic .
- This mini-review discusses some of the possible safe recommendations related to BCG intravesical bladder treatment.
- In addition, we managed to discuss several factors that would affect our decision for service provision, namely BCG shortage, availability of staff, and Personal Protective Equipment logistics.
- The objective of this review is to discuss a possible challenging issue regarding the overlapping picture of fever in the form of a BCG side effect versus a presentation of COVID-19.
- These highlights are important to consider for the upcoming next phase of the pandemic, whenever gradual resumption of elective activities becomes an option.

Accordingly, as summarized in Figure 1, there is no uniform consensus regarding such recommendations. Nevertheless, there are several other factors that control intravesical BCG service provision that we need to take into consideration.

For long, even before this COVID-19 crisis, there have been concerns about BCG shortage caused by an increasing global demand for the product. There are some recommendations about how to overcome such a shortage, including using one-half or one-third of BCG dosage, skipping maintenance therapy, or using a preferable alternative (e.g., Mitomycin C).[11]

The need to minimize patients' attendance into hospital premises and to avoid spread of infection are issues to be considered. The possibility of the patient himself/herself having COVID-19 symptoms needs to be investigated through a telephone consultation every time before attending the hospital for BCG instillation. In case of suspected COVID-19, treatment will have to be postponed till the patient is declared safe to proceed.

Intravesical BCG service provision can change according to the availability of the nursing staff, who can be deployed for alternative roles, as well as the logistics of Personal Protective Equipment (PPE).[12]

Meanwhile, urologists need to be aware of the overlapping clinical presentation in case a patient develops fever after intravesical BCG treatment, which is a possible side effect in about 17% to 38% of cases.[4] This can lead to a dilemma in the diagnosis because fever was identified in 43.8% of patients with COVID-19 on presentation.[13] In such a case of doubt for a symptomatic viral infection with fever, non-steroidal anti-inflammatory drugs should be avoided, and paracetamol (acetaminophen) should be prescribed instead.[14] To avoid misdiagnosis, these patients need to be managed in isolation till a definite diagnosis is confirmed.

When the first wave of this pandemic is behind us, the pent-up patient demand for such procedural care may be immense, and healthcare organizations, physicians, and nurses must be prepared to meet this demand. Many patients have had their needed, but not essential, procedures postponed because of the pandemic. In the upcoming second phase of the global pandemic, we (urologists) need to take into consideration all the aforementioned points.

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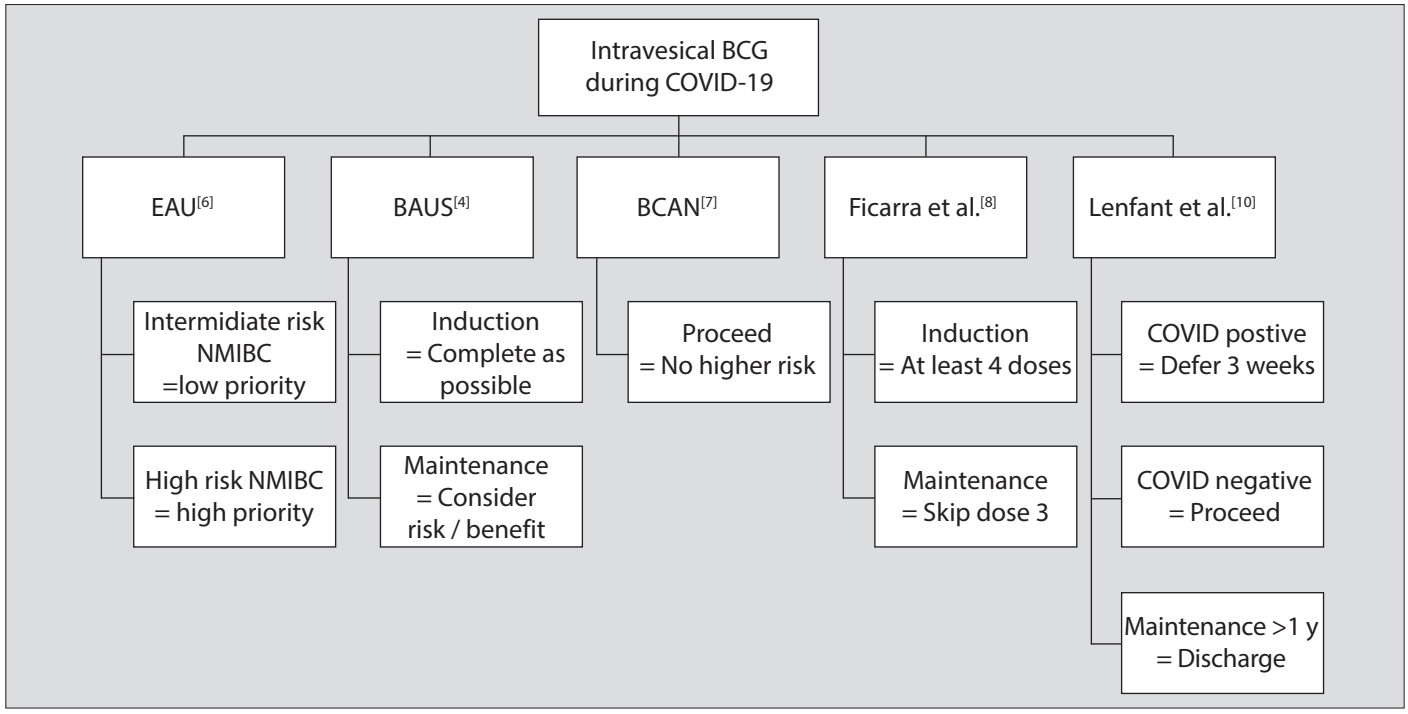

Figure 1. Summary of recommendations for intra-vesical BCG treatment during COVID-19 pandemic

Conclusion

To date, during COVID-19 pandemic, there has been no evidence that intravesical BCG treatment poses any specific risk for contracting the infection. Nevertheless, we need to take into consideration the availability of BCG, nursing staff, and PPE as well as the risk of spreading the infection and the overlapping picture of side effects after BCG adjuvant treatment. This is crucial to consider not only during the current phase of COVID-19 but also for the upcoming next phase of the pandemic.

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