Intravesical BCG: Possible Protective Impact Against COVID-19 in NMIBC Patients

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Abstract

Purpose: To determine the incidence of COVID 19 in a series of registered patients with non-muscle invasive bladder cancer, treated by TUR-BT and intravesical BCG. Patients and method: We analysed 127 patients with non-muscle invasive bladder cancer, in the medium/high risk group, registered between 2001-2020. The patients and families have been contacted by phone. In this interval, 32 patients deceased (cardiovascular pathologies, non-urologic neoplasia, tumour progression), 95 patients are still alive, 24 women and 71 men. The average age was 61.7 (16-86), the majority being over 50, included in the high-risk group for COVID-19. The patients were resected endoscopically and received a cytostatic instillation within the first 6 hours. Reresection of the tumour bed was practiced in pT1 patients. The adjuvant treatment with BCG was used in the induction form at each relapse and maintenance (22 patients), respectively. Until 2005, we used the local strain (Cantacuzino Clinical Institute), after that, the strain from Bulgaria (Calgevax) and Medac (Germany). Results: 95 patients are still alive. Tumour relapses were registered in 34 patients. 3 patients registered tumour progression, resolved through radical cystectomy (2) and irradiation. In 3 cases, upper tract urothelial tumours were registered (nephroureterectomy with perimeatic cystectomy). 63 patients underwent induction treatment, while 22 underwent maintenance treatment. Complications: Intolerance to BCG in 4 patients, BCG cystitis in 5 patients, arthritis in 1 patient, septic status in 2 patients. In the analysed batch of patients, no COVID-19 cases have been registered. Conclusions: It appears that the intravesical administration of BCG represents an immunologic booster (confirmable through PPD), resulting in a reduction of the COVID-19 infection incidence.

Keywords: COVID-19, bladder cancer, BCG.
The patients or families have been contacted by phone. In this interval, 32 patients deceased (cardiovascular pathologies, non-urologic neoplasia, tumour progression), 95 patients are still alive, 24 women and 71 men. The average age was 61.7 (16-86), the majority being over 50, included in the high-risk group for COVID-19. The patients were resected endoscopically and received a cytostatic instillation within the first 6 hours. Reresection of the tumour bed was practiced in pT1 patients. The adjuvant treatment with BCG was used in the induction form at every relapse and maintenance (22 patients), respectively. Until 2005, we used the local strain (Cantacuzino Clinical Institute), after that, the strain from Bulgaria (Calgevaz) and Medac (Germany).

**RESULTS**

95 patients are still alive; 16 patients were pTa, but high risk, 75 patients were pT1, 4 patients were pT2. The tumour relapses were registered in 34 patients. 3 patients registered tumour progression, requiring radical cystectomy (2) and irradiation, respectively. In 3 cases, upper tract urothelial tumours were registered (nephroureterectomy with perimeatic cystectomy). 63 patients underwent induction treatment, while 22 underwent maintenance treatment (12-36 months).

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**DISCUSSIONS**

In adults, BCG vaccination is unable to offer complete protection against pulmonary tuberculosis, with an efficiency range between 0 and 80%7,9, which ex-
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plans why TB is one of the major causes of mortality worldwide. Evidence suggests that the BCG vaccine may offer a long-term protection until 15-20 years\textsuperscript{10,11}. Consequently, it was assumed that the protective effect of the BCG vaccine is likely to last for 15 years, without reducing the efficacy of the vaccine within this period\textsuperscript{12,13,14,15}.

BCG vaccination during childhood and teenage induces the immunologic memory to tuberculosis antigens, which are still present and measurable in the majority of vaccinated persons\textsuperscript{16}. BCG protection may decrease in time since vaccination. A study from Norway, conducted over 41 years on patients between 12-50 years old, shows different protection numbers: an average of 49% efficiency of the BCG vaccination\textsuperscript{18}.

In case of previously vaccinated persons, the recent studies showed that the re-vaccination is safe, well tolerated and is not associated with an increased frequency or severity of the local or systemic reactions, as compared to the primary BCG vaccination\textsuperscript{11}. On the other hand, the revaccination might extend the protection duration against tuberculosis infection, offered by BCG, assertion confirmed through the tuberculin test.

Studies showed that anti TB antibodies titre (gamma interferon range) objectified through the tuberculin test (PPD) and with role in the protection against tuberculosis infection, evokes extremely different.

In children, it is maintained at 75%, in adults at 50% and may oscillate between 0 and 80%.

In countries at risk, boosters are carried out1-2 in teenagers and at 18 years old (first vaccination is administrated during suckling).

Three new clinical trials started recruiting for testing the hypothesis according to which the BCG vaccination may protect against COVID-19 in healthcare workers. Clinical trials in Australia ("BRAVE", PI Curtis), USA ("BADAS", PI: Kamat, Dinardo) and the Netherlands (PI: Netea) intend to randomise cumulatively 6,000 workers in the health field for BCG vaccination against a placebo agent\textsuperscript{19,20,21,22}. Another case-control observational study in Egypt started to recruit COVID-19 positive patients to compare the severity of the disease in patients tested positive for BCG with negative ones\textsuperscript{12}.

Regarding patients who benefit from intravesical BCG therapy for bladder cancer, the potential effects of this treatment on COVID-19 are not clear. The mechanism of action following the vaccination and intravesical administration differs significantly\textsuperscript{13,14}. BCG, apart from the local effect, appears to have a systemic effect with impact on the acquired immunity. Our hypothesis is that the intravesical instillations represent a clear booster inducing the control of the cytokine storm syndrome, involved in COVID-19 morbidity.

A BCG phial used for bladder cancer is 500 times higher than the dose necessary for vaccination, another quantitative element justifying the systemic answer. Approximatively 40% of patients with intravesical BCG induction become positive to the PPD test. There are studies showing that for this reason, patients became immune to tuberculosis, due to BCG inductions.

Webinar Ashim Kamat\textsuperscript{22}.

CONCLUSIONS

It appears that the intravesical administration of BCG represents an immunologic booster (confirmable through PPD), resulting in a reduction of the COVID-19 infection incidence.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

References


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