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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.

Rezumat

Scop: Stabilirea incidenței COVID -19 la pacienții care sunt în evidența clinicii cu cancer non-invaziv de vezică urinară, tratați prin TURV și BCG intravezical. **Pacienți și metodă:** Am analizat 127 de pacienți cu tumori non-invazive ale vezicii urinare, în grupa de risc mediu/ mare, luați în evidență între 2001-2020. Pacienții sau familiile au fost contactate telefonic. În acest interval au decedat 32 de pacienți (patologie cardiovasculară, neoplazii non-urologice, progresie tumorală), 95 de pacienți sunt în viață: 24 de femei și 71 de bărbați. Vârsta medie a fost de 61,7 (16-86) ani, majoritatea cu vârsta peste 50 de ani în grupa de risc mare pentru COVID-19. Pacienții au fost rezecați endoscopic și au primit o instilație cu citostatic în primele 6 h. La cei în pT1, s-a practicat rerezecția patului tumoral. Tratamentul adjuvant cu BCG s-a folosit în forma de inducție la fiecare recidivă, respectiv întreținere (22 de pacienți). Până în 2005 am utilizat tulpina autohtonă (IC Cantacuzino), apoi cea din Bulgaria (Calgevax) respectiv Medac (Germania). **Rezultate:** 95 de pacienți sunt în viață. Recurențe tumorale s-au înregistrat la 34 de pacienți. 3 pacienți au avut progresie tumorală, soluționată prin cistectomie radicală (2) respectiv prin iradiere. În 3 cazuri au dezvoltat

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tumori de uroteliu înalt (nefroureterectomie cu cistectomie perimeatică). Tratament de inducție au făcut 63 de pacienți, tratament de întreținere 22. **Complicațiile survenite:** intoleranță la BCG 4 pacienți, cistită BCG 5 pacienți, artrită 1 pacient, stare septică 2 pacienți. În lotul de pacienți analizat nu au fost cazuri de COVID-19. **Concluzii:** Se pare că și administrarea intra vezicală a BCG constituie un rapel imunologic (confirmabil prin PPD), rezultând o reducere a incidenței COVID-19.

Cuvinte cheie: COVID-19, cancer de vezică, BCG.

Abbreviations

BCG - Bacillus Calmette-Guérin

COVID-19 - Corona Virus Sars 2

NMIBC - Non muscle invasive bladder cancer

PPD - Purified Proteine Derivative

TB - Tuberculosis

Bacillus Calmette-Guérin (BCG) has been used for almost a century (since 1921) to prevent the tuberculosis infection. Countries with a national BCG vaccination program for the entire population appear to have a reduced incidence and death rate due to COVID-19. This might be explained by the known benefits of the immunity acquired through BCG vaccination. In countries where the BCG vaccination program has been paused (Italy, France, The Netherlands) the morbidity due to COVID-19 is clearly different from other countries, where the vaccination is commonly practiced (countries from the Eastern Europe).

COVID-19 incidence was 0,8/ millions inhabitants in countries with BCG vaccination programs and 34,8/ millions inhabitants in countries without vaccination programs. Also, the mortality amounted to 0.08 in countries with BCG vaccination and 34,8 in countries without vaccination program^{1,2,3,4}.

In the absence of a specific vaccination against COVID-19, the BCG vaccination based on population may play a role in reducing the impact of such disease⁵.

The BCG vaccination decreases the rates of infection with pneumonia, staphylococcus aureus and plays an important role in the protection against viruses, such as influenza, yellow fever and herpes⁶.

PATIENTS AND METHOD

Patients and methods. We analysed 127 patients with non-muscle invasive bladder cancer, in the medium/high risk group, registered between 2001-2000.

The patients or families have been contacted by phone. In this interval, 32 patients deceased (cardiovascular pathologies, non-urolologic 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 (Calgevas) 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).

Complications: intolerance to BCG in 4 patients, BCG cystitis in 5 patients, arthritis in 1 patient, sepsis in 2 patients.

In the analysed batch of patients, no COVID-19 cases have been registered.

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-

plains 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^{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^{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 persons¹⁶. 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 vaccination¹⁸.

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 vaccination¹¹. 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, evolves 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 out 1–2 in teenagers and at 18 years old (first vaccination is administered 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 cumulat-

ively 6.000 workers in the health field for BCG vaccination against a placebo agent^{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 ones¹².

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^{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. Approximately 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 Kamat²².

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.

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