







ORIGINAL PAPER

COVID-19 infection threat in patients with high-risk non-muscle invasive bladder cancer receiving intravesical BCG therapy

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Abstract

Aim: We evaluated the COVID-19 infection threat in patients receiving intravesical BCG therapy which has immunotherapeutic effects and is of vital importance in most of the individuals with high-risk non-muscle-invasive bladder cancer (NMIBC) and investigated the need for postponement of this therapy.

Methods: A total of 71 patients, who were diagnosed with high-risk NMIBC and on intravesical BCG treatment regularly (induction or maintenance), were enrolled in the study. The patients were classified into two groups depending on whether they were diagnosed with COVID-19 during the pandemic period or not.

Results: Of 71 patients, 26 underwent a COVID-19 polymerase chain reaction test with clinical suspicion during the pandemic period. Of these 26 patients, 4 were diagnosed with COVID-19. Age of the patients, working status (working/retired), compliance with containment measures against the pandemic, number of BCG courses, adverse effects after BCG therapy and systemic immune-inflammation index, which is an inflammation-related parameter, were not different between groups ($P > .05$). Neutrophil/lymphocyte ratio was significantly higher in the COVID-19 positive group ($P < .05$). COVID-19 positivity was higher in age groups 50-64 (6.6%) and 65-80 (5.8%) years than that in similar age groups of the normal population.

Conclusion: Every effort should be made to administer intravesical BCG treatment in high-risk NMIBC patients even during the pandemic period. However, increased risk of COVID-19 transmission should be kept in mind and protective measures against COVID-19 for healthcare providers and patients before the procedure should be taken optimally. The procedure should be postponed in patients with lymphopenia in recent complete blood count.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), which was first reported on January 7th in 2020 as a result of investigations from pneumonia cases of unknown aetiology in Wuhan, China's Hubei province, caused a pandemic all over the World.¹ The disease is transmitted mainly

through droplets. Asymptomatic individuals might be infectious, because the virus could be detected in their respiratory secretions. First COVID-19 case was announced on March 13th in Turkey and over 200,000 laboratory confirmed cases were reported until June 6th.²

COVID-19 pandemic resulted in postponement of lots of medical and surgical procedures. The rationale behind this approach was

decreasing the risk of COVID-19 transmission, increasing bed availability for COVID-19 in wards and intensive care units, relieving the health care providers of workload except COVID-19 and limiting the aerosol generating procedures. Several guidelines stratifying urological procedures into risk groups developed recommendations about which procedure should be carried out or postponed.^{3,4} Postponement of intravesical bacillus Calmette-Guérin (BCG) therapy in patients with high-risk non-muscle invasive bladder cancer (NMIBC) is not recommended in present studies.^{5,6} Although increased COVID-19 transmission risk in patients receiving intravesical BCG is speculated in the abovementioned studies, there are no sufficient studies to compare risk of transmissions among treatment receiving patients and normal population. In this study, COVID-19 infection threat is evaluated in patients receiving intravesical BCG therapy which has immunotherapeutic effects and is of vital importance in most of the individuals with high-risk non-muscle invasive bladder cancer (NMIBC) and the need for postponement of this therapy is investigated.

2 | MATERIALS AND METHODS

This study was approved by the local Ethics Committee (Hamidiye-BAEK 20/299) and conducted according to the principles of World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

In Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey, patients who were diagnosed with high-risk NMIBC from 2018 to 2020 and on intravesical BCG treatment regularly (induction or maintenance), were enrolled in the study. During the pandemic, intravesical BCG treatment and cystoscopy controls were continued according to the European Association of Urology guideline recommendations for patients with bladder cancer.⁷ Up-to-date data of the most patients were obtained by the Uro-oncology outpatient clinic checks in July 2020 and the rest by telephone conversation retrospectively. Exclusion criteria were having any missing data in records or analyses, refusal to enrol in the study, not receiving intravesical BCG therapy regularly, incompleteness of at least 6-week intravesical BCG induction, having chronic lung diseases which increases COVID-19 risk and being immunosuppressed due to a systemic disease or a medical treatment.

Gender and age of the patients, occupations and status (working or retired), compliance with containment measures against pandemic, number of intravesical BCG courses, adverse effects after BCG treatment, COVID-19 infection in the patients and their household members and severity and inpatient/outpatient status of the positive individuals were collected. Recent total blood count results before pandemic (January-March, 2020), neutrophil/lymphocyte ratios (NLR) and systemic immune-inflammation indices (SIIs) (calculated according to $SII = \text{neutrophil} \times \text{platelet/lymphocyte formula}$) of the patients were recorded. The patients were analysed by classifying into two groups depending on whether they were diagnosed with COVID-19 or not. Our COVID-19 incidence in patients receiving intravesical BCG therapy was compared with that in the

What's known

- Coronavirus 2019 disease affected the oncological approaches in uro-oncology and caused to delay of surgical treatment for all cancer types due to pandemia.
- Intravesical BCG treatment has not performed in the world due to COVID-19 disease and caused to suboptimal treatment for patients with high-risk non-muscle-invasive bladder cancer.
- Although increasing risk due to BCG treatment, society of uro-oncology recommended that BCG treatment could be carefully performed.

What's new

- This is the first study in the literature that reports of increasing risk due to BCG treatment on COVID-19 pandemia in patients with high-risk non-muscle-invasive bladder cancer.
- We recommended that lymphopenia may be routinely evaluated before the BCG treatment courses.

corresponding age groups of the normal population demonstrated in COVID-19 Daily Situation Report Turkey (June 29th, 2020) provided by Ministry of Health.²

2.1 | Statistical analysis

Data analyses were performed using SPSS Statistics 20.0 software (SPSS Inc, Chicago, IL, USA). The normality hypothesis was tested using the Kolmogorov-Smirnov test during data analysis. Quantitative variables were expressed as mean (standard deviation) or as median (interquartile range) according to normality test results. Qualitative variables were expressed as presence or absence percentage and Chi-square test was applied. Mann-Whitney's *U* test was used to evaluate all non-normally distributed variables and *T*-test was used to evaluate all normally distributed variables. A $P < .05$ was considered statistically significant in all analyses.

3 | RESULTS

A total of 71 patients, 4 of whom were female, were enrolled in the study. Mean age of the patients was 65.61 ± 9.46 years and 59 of them were retired. Mean self-assessed compliance with pandemic containment measures (staying at home, wearing facial masks, good hygiene) was $91.33 \pm 11.77\%$. Mean, minimum and maximum numbers of course for BCG were 11.46 ± 5.72 , 6 and 27, respectively (Table 1). Secondary complications due to intravesical BCG therapy were encountered in 22 patients, 4 of whom were hospitalised because of BCG sepsis.

Polymerase chain reaction (PCR) test for COVID-19 was performed in 26 of 71 patients with clinical suspicion during the pandemic period. Of those, four were diagnosed with COVID-19. Of positive individuals, three were hospitalised and one was treated at home-quarantine. All of these patients survived. In remaining 45 patients, neither PCR test for COVID-19 was performed nor any prophylactic treatment was administered as a result of absence of clinical suspicion. Household members of 11 patients were diagnosed with COVID-19 and 2 of them were hospitalised. In 12 of 71 patients, computed tomography (CT) of the thorax was carried out and no viral pneumonia findings were detected except the four patients, who were diagnosed with COVID-19.

The patients were classified into two groups depending on whether they were diagnosed with COVID-19 or not. Age of the patients, working status (working/retired), compliance with containment measures against pandemic, number of BCG courses, adverse effects after BCG therapy and SII, which is an inflammation related parameter, were not different between groups ($P > .05$). NLR was significantly higher in COVID-19 positive group ($P < .05$) (Table 2).

In subgroups analyses by age, COVID-19 positivity was higher in our patients in 50-64 and 65-80 years subgroups (6.6% and 5.8%, respectively) in comparisons with the incidences of the corresponding age groups of the normal population demonstrated in COVID-19 Daily Situation Report Turkey (June 29th, 2020) provided by Ministry of Health (Table 3).

4 | DISCUSSION

Mechanism of COVID-19 infection is binding of virus angiotensin-converting enzyme 2 (ACE2) receptor and entering to host cells.⁸ Patients on ACE inhibitors have greater expression of ACE2 receptors which is shown to be the entry point into human cells for COVID-19 virus. This leads to the corollary that any drug or vaccine which has the potential to increase the level of ACE may help down regulate the expression of ACE2 receptors, thereby having some

beneficial effect on the host immune system against COVID-19. Earlier animal studies have shown that ACE-like activity increased with inflammation induced by BCG suppressed the induction of the inflammatory response in both lungs and spleen.⁹ Consequently, the BCG vaccine does not directly protect against the coronavirus but provides a boost to the immune system which may lead to improved protection and a milder infection.¹⁰

Countries which have universal long-standing policies of BCG vaccination were less severely affected from COVID-19 compared with those without universal policies of BCG vaccination (ie, Italy, the Netherlands and the United States).¹¹ Countries which have a late start of universal BCG policy (Iran, 1984) had high mortality, consistent with the idea that BCG protects the vaccinated elderly population.⁹ Therefore, recently, researchers hypothesised that BCG vaccination might also combat COVID-19 because of its broad ability to stimulate the immune system. However, it should be emphasised that the causality is not yet proven; there is only one study predicting an association.¹²

Intravesical BCG treatment (application of attenuated Mycobacterium Bovis vaccine through urethra into the bladder) acts by massive local immune response. Adhesion of BCG to the urothelium including malignant cells induces secretion of cytokines and chemokines which results in migration of different immune system cells to the bladder wall.¹³ By cellular immunity, phagocyte activation and new cytokine environment and by humoral immunity direct immune response of CD4 + T cells with differentiation to TH1 and/or TH2 cells are stimulated.¹⁴ Beside the local immunotherapeutic effects of intravesical BCG, systemic immunological effects are also shown.¹⁵ Intravesical BCG induces an important systemic impact as humoral response and increases IgG level binding to tuberculin and mycobacterial heat shock proteins (HSPs).^{16,17} Although these findings are in favour of the hypothesis that the immunotherapeutic effect of intravesical BCG therapy for patients with NMIBC during COVID-19 pandemic might be protective against COVID-19 infection per se, our results did not support this.

TABLE 1 Demographic data and laboratory findings of the patients with NMIBC receiving intravesical BCG

	Min-Max	Mean \pm SD
Age (y)	34-86	65.61 \pm 9.46
Adaptation to pandemic precaution	30-100	91.33 \pm 11.77
Number of course for BCG	6-27	11.46 \pm 5.72
Neutrophil Count ($10^3/\text{mm}^3$)	1.83-9.32	4.68 \pm 1.66
Lymphocyte Count ($10^3/\text{mm}^3$)	0.72-4.77	2.26 \pm 0.81
Platelet Count ($10^3/\text{mm}^3$)	74-460	235.88 \pm 72.66
NLR	0.97-8.75	2.41 \pm 1.19
SII	154-2013	564.02 \pm 314.59

Abbreviations: NLR, neutrophil lymphocyte ratio, SII, systemic immune-inflammation index.

	COVID-19		P
	(-)	(+)	
	Mean ± SD	Mean ± SD	
Age (y)	65.67 ± 9.75	64.75 ± 3.3	.85 ^a
Adaptation to pandemic precaution	91.41 ± 11.99	90 ± 8.1	.489 ^b
Number of course for BCG	11.55 ± 5.73	9.25 ± 2.62	.686 ^b
NLR	2.29 ± 0.96	4.02 ± 3.18	.04 [*]
SII	554.1 ± 307.16	590 ± 579.19	.439 ^b
Retired n (%)			
No	11 (%16)	1 (%25)	.656 ^c
Yes	56 (%84)	3 (%75)	
History of adverse effects of BCG n (%)			
No	47 (%70)	2 (%50)	.397 ^c
Yes	20 (%30)	2 (%50)	

Abbreviations: NLR, neutrophil lymphocyte ratio; SII, systemic immune-inflammation index.

^aT Test.

^bMann-Whitney U Test.

^cChi-Square.

*P < .05.

TABLE 3 COVID-19 rates in study cohort and normal population in subgroups by age

Age (y)	n	COVID-19 (+) rate (%)	COVID-19 (+) rate in population (%) ^a
25-49	2	—	0.63
50-64	30	6.6	0.58
65-79	34	5.8	0.55
80+	5	—	0.7

^aCOVID-19 Daily Situation Report Turkey (June 29th, 2020) provided by Ministry of Health (<https://covid19.saglik.gov.tr>).

It is supposed that patients, who sustained cancer or are being treated for cancer, are in risky group for COVID-19.^{18,19} Of cases until January 31st, 2020 in China, 1590 (1%) had a cancer diagnosis and this rate was higher than that of general population in China (0.29%).²⁰ The most important parameter with a five-fold increased risk in this study was receiving chemotherapy or undergoing surgery in last month. In a study from 14 centres from China comparing 105 patients, who had cancer, with 536 patients without cancer, increased risk with cancer especially hematologic malignancies, lung cancer and metastatic cancer is reported.²¹ To the best of our knowledge, there is no study regarding COVID-19 incidence in patients with early stage bladder cancer in English literature. COVID-19 incidence in our patients receiving intravesical BCG due to high-risk NMIBC was 5.6% and higher than that of general population. Among parameters which might increase the risk, NLR was significantly higher in COVID-19 positive group.

TABLE 2 Observed parameters in COVID-19 (-) and COVID-19 (+) groups

In our three hospitalised patients due to COVID-19, lymphocyte levels were below $1.5 \times 10^3/\text{mm}^3$. However, this result might be due to small patient group of our single-centre study. Intravesical chemotherapy, which is advised for low- and some intermediate-risk NMIBC and has lower complication rates than BCG therapy, is not recommended during pandemics because it could increase the complication rates in the postoperative period and prolong the length of hospital stay.^{22,23} However, according to recent uro-oncology guidelines for COVID-19 pandemic period, intravesical BCG treatment should not be postponed providing that the clinic has adequate conditions considering the potential benefits to patients regarding high-risk NMIBC versus probable complications.^{3,4} Teoh and colleagues advocated that for patients with high-risk NMIBC, benefit of continuing BCG for a better cancer control outweighed the potential risk of COVID-19 infection along the treatment course, in their article published in *World J Urol*.⁵ In the same article, they concluded that it can be interrupted during pandemic period in high-risk NMIBC patients who completed minimum 1-year BCG treatment and in intermediate-risk ones, despite the lack of relative oncological data. We think every effort should be made to administer intravesical BCG treatment, which is the most effective therapy for preventing recurrence and progression of the disease in patients with high-risk NMIBC, even during COVID-19 pandemic. However, increased risk of COVID-19 transmission should be kept in mind and protective measures for COVID-19 for healthcare providers and patients before the procedure should be taken optimally. The procedure should be postponed in patients with lymphopenia in recent complete blood count.

5 | CONCLUSION

While clinical researches against the global health crisis due to COVID-19 are still in progress, role of BCG vaccine in alleviation of the disease is put forward. In this study, we recommend being aware of increased risk of COVID-19 transmission in high-risk NMIBC patients receiving intravesical BCG, taking protective measures against COVID-19 for healthcare providers and patients before the procedure optimally and postponement of the procedure in patients with lymphopenia in recent complete blood count.

DISCLOSURE

Authors declared no conflict of interest.

ETHICAL APPROVAL

This prospective descriptive study was approved by the University of Health Sciences Hamidiye Scientific Research Ethics Committee (Hamidiye-BAEK 20/299).

PATIENTS' CONSENT

Informed consent is not obtained from patients to publish the data concerning this study.

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