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Research Article

Treatment of Non-Muscle Invasive Bladder Cancer with BCG: Implications for the SARS CoV-2 Pandemic

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ABSTRACT

Background: Hypotheses defend BCG being able to have an impact on the course of COVID-19 disease, decreasing the rate of infections and their severity.

Objective: To determine if the incidence and severity of COVID-19 are less in patients who receive adjuvant treatment with intravesical BCG for non-muscle invasive bladder cancer and if the number of instillations are influential.

Methods: All the participants treated with intravesical BCG between January and June-2020 were analysed, researching if they had been infected, and comparing them with the infection rate in the general reference population of our Hospital. Ethical Aspects: The Healthcare Ethics Committee of the Hospital approved the study and informed consent forms were delivered to patients treated with BCG in order to authorize the use of their data in this study. Statistical Analysis: OpenEpi (Link) statistical analysis was carried out by means of 2x2 tables applying the chi-square statistic and Fisher test for qualitative variables.

Results: 117 patients, 23 women (19.7%) and 94 men (80.3%), received treatment with BCG. The mean age was 72.12 years; all ≥ 50 years. Seven in induction phase, 6 weeks, and 110 in 1-year maintenance, 3 weeks to 3, 6 and 12 months, excluding those that had < 4 instillations. Three patients (2.56%) were infected with moderate disease that required admission to the ward. None in the Intensive Care Unit. In the general population, 8558 (5.7 %) were infected. 2015 (1.35%) required admission to the ward and 185 (0.12%) in the Intensive Care Unit. There are no statistically significant differences in the infection rate. Neither was there any in the incidence of moderate or severe disease nor in the incidence of disease between the different phases of the intravesical treatment.

Conclusion: We have not been able to demonstrate that intravesical BCG impacts the incidence rate or the severity of COVID-19.

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Introduction

Bladder cancer is an important problem of public health since it is the fifth most frequent cancer in Spain and occupies ninth place worldwide

[1]. Within bladder cancer, the non-muscle invasive form is the most common type diagnosed. As an adjuvant treatment in high-risk patients, to reduce recurrence and tumor progression, vesical instillations with Bacillus Calmette-Guerin (BCG) are done, which strengthen the

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acquired immune response [2-4]. The classic plan consists of a six-week induction cycle, weekly instillation, followed by maintenance with three instillations weekly at 3, 6 and 12 months from the first induction cycle, being able to reach at three years every six months [5, 6]. In our patients, due to the low availability of BCG worldwide, the maintenance was done during only one year. The SARS CoV-2 (COVID-19) disease was declared by the WHO as a pandemic on 11 March 2020 with updated data of 178,870,559 confirmed cases and 3,875,067 deaths (2.1%) [7, 8]. The intensity of the disease and the fatality rate varied in different parts of the world. One of the causes may be the immune differences of each country due to disparities of the world vaccination schedule [6].

There are risk factors that favour its severity, age >60 years, smoking, diseases such as diabetes, high blood pressure, heart disease, chronic lung disease, cerebrovascular diseases, chronic kidney disease, immunosuppression and cancer [9, 10]. There exists a great interest in ascertaining the relationship between the immunotherapy provided by BCG and its effect against the COVID-19 disease. The BCG vaccine has an action mechanism that strengthens the type TH1 immune response (associated with the immune hyperresponsiveness provided by virus as would be the case of SARS CoV-2) [6, 11]. This fact could be verified in a clinical trial in which two groups were randomly divided in which one received a placebo and the other the BCG vaccine. Then all the participants received an intramuscular injection of the seasonal influenza vaccine. Those patients that had received the BCG vaccine obtained a higher immune response (measured through viremia and IL6 and Interferon gamma antiviral response) than those that had not received it [6, 12]. In a clinical trial conducted in South Africa, a group of persons were injected with the BCG vaccination and another with a placebo. The safety of the vaccination was evaluated as a secondary objective, recording the infection rate associated with its use and it was observed that there was a reduction of 73% of infections of the respiratory tract in comparison with the group that had not received it [8, 13].

A clinical trial from Whardhana in Indonesia studied the efficacy of the BCG vaccine, evaluating the prevention of acute infection of the upper respiratory tract, the interferon gamma level and that of IL-10 in the BCG group and placebo [14]. A significant reduction was observed in the number of respiratory tract infections in the BCG group. There are clinical trials in progress with the BCG vaccine as a possible protector against the COVID-19 disease [6, 15]. Four of them, with the population formed by healthcare personnel, intend to demonstrate an improvement in immunity protecting the healthcare workers, NCT04327206 (BRACE) carried out in Australia, NCT04328441 (BCG - CORONA) in the Netherlands, NCT04348370 (BADAS) in the United States, and NCT04350931 in Egypt [16-19]. These studies are going to analyse the rate, the number of days with symptoms and the hospital admittances related to COVID-19. In some countries, the recommendation of vaccinating with BCG has been made despite not yet having a solid scientific basis to support this recommendation [6]. The differences in rate and impact of the disease in different countries have also been studied, highlighting a milder effect in those countries in which the BCG vaccine is included in the vaccination schedule [6]. In our study, we want to analyse if there exists a protector effect of the intravesical BCG against the SARS CoV-2 infection, both in number of infections and in the severity of the symptoms [20]. Furthermore, it would serve to support

the maintenance of treatment with BCG in patients diagnosed with non-muscle invasive bladder cancer while the pandemic lasts.

Hypothesis

Patients diagnosed with non-muscle invasive bladder cancer treated with intravesical BCG have been able to develop a protector effect against the COVID-19 disease.

Primary Objective

To verify if there are differences in the rate of the COVID-19 disease in our sample of patients with non-muscle invasive bladder cancer treated with intravesical BCG in comparison with the reference population of the area of influence of the Hospital, with similar characteristics (≥ 50 years) who do not receive treatment with intravesical BCG.

Secondary Objectives

To compare if there are differences in the moderate and severe infection rate in our sample of patients with intravesical BCG in comparison with the infected patients of the reference population of our Hospital with similar characteristics (≥ 50 years) who do not receive treatment with intravesical BCG. To compare if there are differences in the rate according to the treatment phase in which the patients are found (induction or maintenance).

Patients and Methods

All the patients diagnosed with non-muscle invasive bladder cancer in the period that goes from January to June 2020, without limits of age, race or sex, selecting only those that had received at least four instillations of BCG by considering this figure as the minimum necessary to develop its immune protection effect [21]. We obtained information related to data on SARS CoV-2 infection in order to calculate the rate of COVID-19 cases. We also checked if there had been admittances to hospital wards or to the Intensive Care Unit (ICU) due to SARS CoV-2 infection in order to verify the rate of moderate and severe cases in this group. In addition, information was gathered on the risk factors of COVID-19, age, sex, diabetes, high blood pressure, chronic respiratory disease, heart disease, and obesity. The control population is the population ≥ 50 years from the healthcare coverage area of our Hospital. The data on the number of inhabitants and those of SARS CoV-2 infection were obtained from the population records [22]. The hospital admittance data in wards and in ICU of this group were obtained from the admittance records of the Hospital.

A statistical analysis was conducted to compare the groups with the OpenEpi application (Link), using 2×2 tables applying the chi-square statistic and Fisher test for qualitative variables. Our null hypothesis is that there are no differences in cases of SARS CoV-2 infection between our group of patients in treatment with intravesical BCG and the reference population. The alternative hypothesis would be that there indeed exist differences between both groups using a statistical significance level of 0.05.

Results

One hundred seventeen (117) patients were found in treatment with BCG in this time period, 23 women (19.7%) and 94 men (80.3%). The most numerous age range was that between 70 and 79 years, constituting 41.02%. The median age was 73 years. Seven patients were in induction treatment and 110 in maintenance treatment. We analysed their comorbidities because they can affect the severity of the symptoms of COVID-19. The group of men is the one that presented a higher number

(1.93 with a standard deviation of 1.2). The infection rate of this group was 3 (2.56%), all men. One in induction treatment (14.3% of those that were in induction), and two in maintenance (1.8% of those that were in maintenance). Our sample of patients with BCG, as corresponds to the age prevalence of the non-muscle invasive bladder cancers, was composed by patients ≥ 50 years. For this reason, we analysed data of the reference population ≥ 50 years in order to have comparable populations. The incidence rate is reflected in (Table 1).

Table 1: Incidence rate in general population ≥ 50 years and BCG grouped by age and sex.

	NUMBER (%) MALE POPULATION	NUMBER (%) FEMALE POPULATION	TOTAL (%) POPULATION	NUMBER (%) MALES WITH BCG	NUMBER (%) FEMALES WITH BCG	TOTAL (%) BCG
50-59	1414 (5.9%)	1664 (6.3%)	3078 (6.1%)	0 (0%)	0 (0%)	0 (0%)
60-69	921 (5.1%)	1017 (4.7%)	1938 (4.9%)	0 (0%)	0 (0%)	0 (0%)
70-79	593 (4.3%)	636 (3.2%)	1229 (3.6%)	2 (4.4%)	0 (0%)	2 (4.1%)
80-89	558 (7.1%)	946 (6.5%)	1504 (6.7%)	1 (5.26%)	0 (0%)	1 (4.1%)
≥ 90	194 (22.29%)	615 (20.5%)	809 (20.9%)	0 (0%)	0 (0%)	0 (0%)
TOTAL	3680 (5.7%)	4878 (5.7%)	8558 (5.7%)	3 (3.19%)	0 (0%)	3 (2.56%)

There is a higher number of infected women than men in the reference population. On the contrary, in our BCG sample, only men were infected. By comparing the incidence rate of the two groups, we obtained a $p=0.1933$ thus we could not reject the null hypothesis. That is, there are no differences between the rate of SARS CoV-2 infection in our sample of patients with intravesical BCG and that of the general population ≥ 50 years. In order to study if there is protection regarding the severity of the infection, we analysed the admittance data of both groups, verifying that there were no statistically significant differences both in admittance in the wards, moderate disease, and in the ICU, severe disease, between the two groups. They are described in (Table 2). We conducted a final analysis in which we compared the incidence rate according to whether at that time they were receiving induction or maintenance treatment. We verified that there were no statistically significant differences ($p=0.343$).

Table 2: Admittances in wards and ICU of the general population and BCG sample.

	Admittances/total population of Bilbao ≥ 50 years	Admittances of BCG sample/total BCG sample	pValue
WARD	2015/149222 (1.35%)	3/117 (2.56%)	0.42
ICU	185/149222 (0.12%)	0/117 (0%)	0.99

Discussion

The recommendations regarding oncological treatments during the pandemic and the tasks related to vaccination with BCG and the disease provoked by the SARS CoV-2 has triggered interest in studying the patients in treatment with intravesical BCG. In the study by Brooks, data were extrapolated from the gross rates of infection by SARS CoV-2 between different countries with active vaccination of BCG compared to those without such vaccination [6]. The observed result calculated on the daily incidence rate of COVID-19 was 0.8/million in countries with an

active vaccination programme in comparison with 34.8/million in countries without this BCG vaccination. In the review of the literature, we only found one paper published recently, in March 2021, that correlated the intravesical BCG and the SARS CoV-2 infection [23]. The results, with 175 patients comparing them with the general population of Chile, concluded that it did not decrease the rate of infection, it was perhaps even higher, but a decrease was observed in the mortality of the patients with BCG. In our study, the incidence rate is greater in the general population (5.23% vs. 2.56%), although it is not statistically significant. The difference with the published study could be due to the fact that we compared patients of the same area, all belonging to the reference population of the Hospital and therefore, they are more homogeneous groups.

As a secondary objective, we studied if there exists protection against the clinically moderate and severe COVID-19 disease. There were more admittances to the hospital wards, considered as moderate disease, in the group with BCG (2.56% vs. 1.36%). This data should be analysed with caution, taking into account that they are patients of advanced age (70-89 years) and concomitant pathologies, since the men in our sample have at least two comorbidities which could have influenced the hospitalization percentage. Despite this, it is not statistically significant. Regarding the incidence rate of severe disease, considered as the admittances to ICU, the percentage of admittances in the general population is greater (0.12% vs. 0%), although this is not statistically significant either. The patients in the maintenance phase should have been more protected than those in the induction phase, by having greater probability of developing a trained immunity. Of the three infected patients, 2 of out 7 were in induction treatment and 1 out of 110 in maintenance treatment. Nonetheless, this result is not statistically significant. Thus, there are no differences according to whether they are in the induction or the maintenance phase. During the pandemic, recommendations were published to decrease the number of instillations or even not to carry out the maintenance cycle in order to avoid an increase in the rate of death and of its severity [24-26]. In our study, it is

shown that it is safe to maintain the same regime of instillations during the pandemic.

This study presents a series of limitations. In the first place, it deals with an observational, retrospective study with a limited number of patients. In the second place, it cannot be ignored that the patients in our study are persons with cancer, and for this reason the recommendations of isolation and protection against the SARS CoV-2 infection were applied more effectively than in the group of the population that was not perceived as a population at risk. Furthermore, while all the patients in treatment with BCG were analysed to learn if they had been infected by SARS CoV-2, the estimate of the infection rate of the general reference population of our hospital can be underdiagnosed for the following reasons: Many cases have been asymptomatic or with mild symptoms for which no active infection diagnostic tests (AIDT) had been conducted on them and in the first weeks of the pandemic, there were no AIDTs available in generalised form and infection diagnostic tests were only carried out on persons who were admitted to the hospital. Current scientific evidence backs the immune protection of the BCG vaccine against respiratory infections, among them probably the SARS CoV-2. In our study, despite the low number of infections among the population with intravesical BCG treatment and with none of the infected patients having to be admitted to ICU, we can conclude that the intravesical BCG treatment does not provide any type of protection against the SARS CoV-2 infection. However, they are not more vulnerable to the infection, for which reason the number of instillations would not have to be limited in order not to put high-risk patients at a greater risk of progression.

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Author Contributions

Conceptualization, Methodology, Validation, Writing - Review and Editing, Final Approval of The Version Submitted: Ana Loizaga-Iriarte; Software, Formal Analysis, Investigation, Acquisition of Data, Writing - Original Draft, Final Approval of the Version Submitted: Sheila Mohamed-El Azzouzi; Design of the Study, Formal Analysis, Writing - Review and Editing, Final Approval of the Version Submitted: David Gonzalo-Aparicio; Visualization, Writing - Original Draft, Final Approval of the Version Submitted: Sofía Rey-Gonzalez; Resources, Acquisition of Data, Final Approval of the Version Submitted: Ana I. Serrano-Gutierrez; Acquisition of Data, Formal Analysis, Visualization, Final Approval of the Version Submitted: Elena Riesco-Paredes; Acquisition of Data, Investigation, Final Approval of the Version Submitted: Sandra San Cayetano-Talegon; Conceptualization, Design of the Study, Project Administration, Management and Coordination Responsibility for the Research Activity Planning and Execution, Supervision, Final Approval of the Version Submitted: Miguel Unda.

Conflicts of Interest

None.

Funding

None.

Ethical Approval and Confidentiality

The Healthcare Ethics Committee of Basurto University Hospital approved the study. The principal researcher signed a confidentiality agreement.

Consent

Informed consent forms were delivered to the patients treated with BCG in order to authorize the use of their data in the study.

Abbreviation

BCG: Bacillus Calmette-Guerin

WHO: World Health Organization

ICU: Intensive Care Unit

AIDT: Active Infection Diagnostic Tests

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