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ORIGINAL ARTICLE

BCG versus COVID-19: impact on urology

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Abstract

Purpose To search for evidence base for using BCG in the fight against COVID-19 and the possible impact of these clinical trials on urology practice.

Methods A literature review about the basis of the ongoing clinical trials using BCG against COVID-19, as well as the use of BCG in urology and if there are any implications of these trials on our practice.

Results Based on data from some epidemiological studies, there are some current clinical trials on the use BCG as a possible prophylactic vaccine against SARS CoV-2 which can affect urology practice. Urologists are already struggling with the global shortage of BCG which can be even more aggravated by such trials. In addition, if the ongoing trials proved the efficacy of BCG as a prophylaxis against COVID-19, this may open the door to more urological research opportunities to question the possibility that intra-vesical BCG, given its systemic immunologic effect, may have been protective to this subgroup of urological patients.

Conclusion The ongoing clinical trials using BCG against COVID-19 can affect our urology practice. We need to stay vigilant to such impacts: BCG shortage and possible new chances for urology research work.

Keywords COVID-19 · Pandemic · Urology · BCG · Bladder cancer

Introduction

The World Health Organization (WHO) declared Europe as the epicenter of the COVID-19 pandemic with Italy having the worst hit. In the United Kingdom (UK), London is the worst affected. Similarly, in the United States of America (USA), New York City is the most affected. Unfortunately, at the time of writing this article, USA has the highest number of cases reported. Meanwhile, COVID-19 has not yet hit the Middle East and North Africa as hard as the rest of the world [1].

Early evidence from the current COVID-19 pandemic suggests that the disease intensity and case fatality rate vary in different parts of the world. Better understanding of the epidemiological characteristics of COVID-19, as to why people living in certain nations are more susceptible, would help us effectively control this pandemic. These insights could potentially aid treatment and vaccine development.

One observational study highlighted that interestingly, the impact of COVID-19 is different in different countries. These differences are attributed to differences in cultural norms, mitigation efforts, and health infrastructure. They proposed that national differences in COVID-19 impact could be partially explained by the different national policies with respect to Bacillus Calmette–Guérin (BCG) childhood vaccination as BCG vaccination has been reported to offer broad protection to respiratory infections [2].

They compared large number of countries' BCG vaccination policies with the morbidity and mortality for COVID-19. They found that countries without universal policies of BCG vaccination (Italy, Nederland, USA) have been more severely affected compared to countries with universal and long-standing BCG policies. Countries that have a late start of universal BCG policy (Iran, 1984) had high mortality, consistent with the idea that BCG protects the vaccinated elderly population [2].

They also noticed that BCG vaccination also reduced the number of reported COVID-19 cases in a country. The combination of reduced morbidity and mortality makes BCG

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vaccination a possible new tool in the fight against COVID-19 [2].

Another recent epidemiological study, interestingly published by two urological consultants as the main authors, reported current national programs of BCG vaccination exist in 131 countries; 21 countries have no current program of national BCG vaccination; and for 26 countries, the status is unknown. Over preceding 15 days, incidence of COVID-19 was 38.4/million in countries with BCG vaccination compared to 358.4/million in the absence of such a program. The death rate was 4.28/million in countries with BCG programs compared to 40/million in countries without such a program [3].

It can be argued that observation/correlation does not mean causation. Authors recognized that these data are observational and based on a single time-point and that there may be several confounding issues such as limited testing and reporting in many countries. However, as these data are derived from 178 countries, the trend is striking and supports the mechanistic data that exists for BCG as a protective agent not only for viral and other infections but also against cancer [3].

"While we expected to see a protective effect of BCG, the magnitude of the difference (almost tenfold) in incidence and mortality (of COVID-19) between countries with and without a BCG vaccination program was pleasantly surprising," said Dr. Ashish Kamat, a co-author of the paper and professor of urologic surgery and cancer research at MD Anderson Cancer Center in Houston, Texas.

They concluded that countries with national program of whole population BCG vaccination appear to have a lower incidence and death rate from COVID-19. This may be due to the known immunological benefits of BCG vaccination. In the absence of a specific vaccination against COVID-19, population-based BCG vaccination may have a role in reducing the impact of this disease and is being studied in a prospective trial [3].

Why BCG vaccine against COVID-19?

It has been postulated that patients with co-morbidities such as diabetes and hypertension which are treated with Angiotensin Converting Enzyme [ACE] Inhibitor drugs are at higher risk for developing severe disease due to COVID-19. Patients on ACE inhibitors have greater expression of ACE 2 receptors which have been 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 ACE 2 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 [4].

BCG vaccine's heterologous beneficial effect against non-tuberculosis infections is well known. Children vaccinated with BCG suffer less from other respiratory illnesses; it is used to treat certain bladder cancers and could protect against asthma and autoimmune diseases such as type 1 diabetes. Researchers want to test whether the tuberculosis vaccine could have a similar effect against the new coronavirus, either by reducing the risk of being infected, or by limiting the severity of the symptoms. 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 [4].

The vaccine works on the innate immune system and produces a memory-like response termed "trained immunity" which helps in faster recognition triggering a quicker inflammatory response. Recent studies also have suggested that it has the potential to protect against experimental infection with yellow fever vaccine strain and to enhance immune responses to other vaccines in general including influenza vaccination [4].

In the case of COVID-19, in addition to infection by the virus itself, some patients have also suffered excessive immune responses, with the uncontrolled production of pro-inflammatory proteins, cytokines in what is now termed cytokine storm. Vaccination, in particular against BCG, might help to better orchestrate this inflammatory immune response, The vaccine acts as a "military exercise in peacetime" so that the body can "fight the enemy effectively in wartime" [4].

Given the safety of the BCG vaccine and its low cost, it is worth considering it as a possible preventive strategy in the interim while other vaccine trials are underway.

Clinical trials

Several clinical trials have been recently launched [5] to investigate the possible protection of BCG vaccine including:

A Dutch research group has initiated a multi-center, randomized controlled trial to study the effects of BCG vaccination on reducing the incidence of adverse events related to SARS-CoV-2 in patients 60 years of age or older.
In Australia, researchers from the Murdoch Children's Research Institute have opened the BCG Vaccination to Protect Healthcare Workers against COVID-19 (BRACE) trial.
BACTIR trial (BADAS study).

This trial was first announced online on 2nd April 2020 in an article titled 'Beyond Bladder Cancer: Bacillus Calmette–Guérin (BCG) Vaccination Revisited as a Strategy to Reduce COVID-19 Related Adverse Events in High Risk Health Care Workers and the Elderly'.

BACTIR (BCG vaccination against SARS-CoV-2 to protect health care workers by enhanced trained immune responses: a randomized controlled trial) is again interestingly pioneered by a group of urological surgeons with Dr. Ashish Kamat from MD Anderson Cancer Center in USA, as the principle investigator. Recently, the scientific name of this randomised multicenter trial has been changed into BADAS study (BCG As Defense Against SARS-CoV-2) [http://bcgbadas.org/].

"We are commencing a study in the near future, initially planned for about 1000 healthcare workers, but with plans to rapidly expand to multiple sites as the demand increases. We will vaccinate healthcare workers at highest risk first, such as those who work in emergency centers, ICUs, and watch for how protective the vaccine proves," said Dr. Kamat.

The general perception in immunology is that innate immunity, as opposed to adaptive immunity, is static and does not adapt to an enhanced functional state. However, it has been challenged with an increasing body of scientific literature indicating enhanced nonspecific protection against infections after previous exposure to certain microbial components [6].

It has been recently proposed that the non-specific effects of BCG are mediated through epigenetic reprogramming of monocytes, a process called trained immunity. Little is known regarding the intracellular events controlling its induction. In an immunologic study, they identified autophagy as a key player in trained immunity. Pharmacological inhibition of autophagy as well as polymorphisms in autophagy-related genes blocked BCG-induced trained immunity. Furthermore, BCG vaccine is also used to treat bladder cancer. Genetic polymorphisms in autophagy-related genes correlated with progression and recurrence of bladder cancer after treatment with BCG therapy. These findings open new possibilities for improvement of future BCG-based vaccines to be used against infections and malignancies [6].

BCG in urology

Bacillus Calmette–Guérin (BCG) has been used to treat non-muscle-invasive bladder cancer for more than 40 years now. It is one of the most successful biotherapies for cancer in use with an initial complete response rates of 55–70% in patients with high-risk stage I bladder cancer. Despite long clinical experience with BCG, the mechanism of its therapeutic effect is still under investigation [7].

BCG is known to induce a robust innate immune response leading to long lasting adaptive immunity. Available evidence suggests that urothelial cells (including bladder cancer cells themselves) and cells of the immune system both have crucial roles in the therapeutic anti-tumour effect of BCG. The possible involvement of bladder cancer cells includes attachment to fibronectin of the bladder wall and internalization of BCG, secretion of cytokines and chemokines, and presentation of BCG and/or cancer cell antigens to cells of the immune system [7].

Immune system cell subsets that have potential roles in BCG therapy include CD4(+) and CD8(+) lymphocytes, natural killer cells, granulocytes, macrophages, and dendritic cells. Bladder cancer cells are killed through direct cytotoxicity by these cells, by secretion of soluble factors such as TRAIL (tumour necrosis factor-related apoptosis-inducing ligand), and, to some degree, by the direct action of BCG. Several gaps still exist in our knowledge that should be addressed in future efforts to understand this biotherapy of cancer [7].

The previously mentioned clinical trials investigating the efficacy of BCG vaccine against COVID-19 can have two main impacts on urology practice:

BCG shortage

Merck & Co., Inc. is the sole maker and supplier of BCG to the United States. They are also the only source of BCG to many other countries around the world. Due to the increasing global demand for BCG treatment and as the only source of Onco TICE BCG in many countries, Merck anticipates this shortage to continue throughout 2020 [8].

Although Merck has boosted its production of BCG by more than 100% and is producing the drug to the fullest extent of their manufacturing capacity, they are not able to sustain the increasing global demand of this product since it is a lengthy and complex manufacturing process. This has led to supply constraints and a BCG shortage [8].

The upcoming clinical trials, although justified by the current evolving pandemic global crisis, may add up to the problem of BCG shortage. This issue has been addressed by Paul Hegarty, urology consultant from BACTIR trial, who said "We reached out for Bladder Cancer Advocacy Network (BCAN) and had patient representatives and representatives of the advocacy as in the study there might be a potential for diverting some of the BCG that is used for bladder cancer patients to the trial and I am really pleased that we have full support not only from patients but also from the officials from BCAN" [5].

On the other hand, the dose needed for intradermal administration of BCG vaccine in an adult is 0.1 ml, meaning that one vial of BCG is enough to vaccinate 10 adults [9]. Compared to using one whole vial of BCG, e.g., TICE

(50 mg) per intravesical instillation per patient, this may provide some reassurance to the impact of such trials on BCG shortage.

The American Urological Association (AUA) recommended the following strategies to help maximize the care for patients with Non-Muscle Invasive Bladder Cancer (NMIBC), in the face of BCG shortage [8]:

I. BCG should not be used for patients with low-risk disease.
II. Intravesical chemotherapy should be used as the first-line option for patients with intermediate-risk NMIBC. Patients with recurrent/multifocal low-grade Ta lesions who require intravesical therapy should receive intravesical chemotherapy such as Mitomycin, Gemcitabine, Epirubicin or Docetaxel instead of BCG.
III. If BCG would be administered as second-line therapy for patients with intermediate-risk NMIBC, alternative intravesical chemotherapy should be used rather than BCG in the setting of this BCG shortage.
IV. For patients with high-risk NMIBC, high-grade T1 and CIS patients receiving induction therapy, they should be prioritized for use of full-strength BCG. If not available, these patients and other high-risk patients should be given a reduced 1/2 to 1/3 dose, if feasible.

(If 1/2 to 1/3 dose of BCG is used, every attempt should be made to treat multiple patients on the same day, while being consistent with product labeling, to avoid drug wastage. It is recommended the practitioners communicate with their pharmacy to ensure that if split dosing is used, it is done with appropriate safety precautions).

V. If supply exists for maintenance therapy for patients with NMIBC, every attempt should be made to use 1/3 dose BCG and limit dose to one year.
VI. In the event of BCG supply shortage, maintenance therapy should not be given and BCG-naïve patients with high-risk disease should be prioritized for induction BCG.
VII. If BCG is not available, a preferable alternative to BCG is Mitomycin (induction and monthly maintenance up to one year). Other options such as Gemcitabine, Epirubicin, Docetaxel, Valrubicin or sequential Gemcitabine/Docetaxel or Gemcitabine/Mitomycin may also be considered with an induction and possible maintenance regimen.
VIII. Patients with high-risk features (i.e., high-grade T1 with additional risk factors such as concomitant carcinoma in situ, lymphovascular invasion, prostatic urethral involvement or variant histology) who are not willing to take any potential oncologic risks with alternative intravesical agents, should be offered initial radical cystectomy, if they are surgical candidates.

Have urologists been immunizing patients even before COVID-19 pandemic?

Most of the time, we focus on the local immunotherapeutic effect of intravesical BCG; meanwhile, its systemic immunologic effect has been already proven.

A study directed toward ascertaining the local histologic changes and systemic serum response to BCG injection in the dog bladder was undertaken in anticipation of its possible application in the treatment of bladder neoplasm. Local response was predictable and was associated with low morbidity. The appearance of serum precipitin bands to culture filtrates of mycobacteria tuberculosis strains strongly suggests systemic absorption and reaction to BCG administered intravesically [10].

Another study found that following initial instillation, cytokine and chemokine concentrations peak within 2–8 h leading to immune cell recruitment to the urothelium. The importance of adaptive immunity is supported with improved 5-year disease free survival of 80% patients with a positive PPD test prior to the initiation of BCG therapy compared to only 45% in patients who were PPD negative prior to the initiation of BCG therapy. This proves that BCG stimulates an innate immune response locally and systemically [11].

A third study showed that intra-vesical BCG induced a significant systemic effect in the form of humoral response, increasing IgG level against tuberclin and mycobacterial heat shock protein (hsp). This antibody response increases gradually till 3 months after completion of 6-weeks BCG course [12].

Accordingly, there is evidence to support the systemic immunologic impact of intravesical BCG rather than sole effect on the bladder. This can raise the question whether it is possible that intra-vesical BCG treatment for NMIBC patients provided them with a beneficial effect in the era of COVID-19 pandemic.

Through its immunomodulatory effect, regulating cytokine response at some level, could intravesical BCG treatment have been protective from cytokine storm syndrome that has been proposed as a pathophysiological mechanism for severe COVID-19 [13] morbidity and mortality?

Is it possible that we urologists have been already immunizing our patients even before the COVID-19 pandemic?

This possibility needs further investigation based on the results of the ongoing trials, e.g., BACTIR trail, first to prove the protective effect of BCG vaccine against COVID-19.

Conclusion

In the face of a global health crisis imposed by COVID-19 pandemic, clinical trials are still ongoing to find a cure. BCG vaccination has been proposed, through epidemiological studies, as having a role in reducing the impact of this disease. Urologists should anticipate more BCG shortage. As well, if proven effective against COVID-19, this may give urologists another field of research to explore the possible protective impact of intra-vesical BCG on NMIBC patients given its systemic immunologic modulatory effect.

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Conflict of interest The author declares that they have no conflict of interest.

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