



COVID-19 research: promising tracks leading to uro-oncology

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Introduction

Since the report of the first cases of pneumonia of unknown cause by the WHO at the close of 2019, the SARS-2 Coronavirus (Sars-CoV-2) and its related disease Covid-19 has spread rapidly all over the globe. According to the online database of the Johns Hopkins University (JHU) by April 20th, 2,411,553 infections, 165,338 deaths and 628,816 recoveries had been confirmed worldwide [1, 2]. The pandemic placed a great burden on health care systems and forced them to change the way they operate. To free up the intensive care capacities, several governments decided to defer most interventions (surgeries) in non-life-threatening conditions, as well as all elective hospital patient visits.

In urological practice, the number of elderly patients with multiple comorbidities is overrepresented, among whom oncologic patients in particular face the greatest risks from Covid-19. Against this background, it is crucial to weight the possible harms caused by delaying therapies against the risk posed by a possible Coronavirus infection. This consideration may be difficult in specific cases of clinical decision-making. Generally, it is recommended to perform curative oncologic surgical interventions only in high-risk cancers without any delay [3]. In case of immuno- and chemotherapy administration, immunosuppressant, neutropenic effects should always be taken into consideration, as these may lead to higher susceptibility to Coronavirus infection, with a higher rate of life-threatening complications. Furthermore, we should mention the risk caused by steroids administered with anti-tumor drugs. In addition to these rather general considerations, there are some aspects of Covid-19 more specific for urologists.

Covid-19 and BCG

First of all, we would like to underline the potential protective effect of Bacillus Calmette Guerin (BCG) vaccination against Covid-19 [4]. There has already been evidence showing that the BCG vaccine not only provides protection against tuberculosis, but also has a so-called heterologous immunomodulatory effect, which results in protection against various viral infections as well [5–7]. Its exact mechanism is not yet fully understood, but involves the activation of both heterologous lymphocytes and the trained immune system resulting in lower rates of neonatal sepsis and respiratory tract infections [5, 6]. Protection of BCG vaccination against viral infections has also been described for Herpes and Influenza viruses [8].

In this context, a recent study aimed to compare the epidemiological data of Covid-19 in countries with ongoing BCG vaccination programs with data from regions where no such program exist [4]. The authors found significantly lower incidence and mortality rates in countries with ongoing BCG vaccination [4].

Certainly, the temporal and geographical differences in the course of virus spread, various testing capacities and reporting of death by or with Sars-CoV-2 can bias results. On the other hand, data from numerous countries have been included in the study potentially reducing the above effect. Differences in prevalence and mortality may be particularly interesting when comparing Portugal and Spain, where geographical proximity provides a better opportunity for comparison. Based on the data provided by Worldometer and JHU as of April 20th, the incidence of Sars-CoV-2 infection is 4249/million people in Spain and 1981/million in Portugal [2, 9]. The case-fatality ratio is 10.29% in Spain and 3.53% in Portugal, respectively [2]. Portugal is among those countries which have an ongoing BCG vaccination program, while Spain's was canceled in 1981 [10]. Based on these findings, the Murdoch Children's Research Institute in Australia and the Radboud University in the Netherland have launched prospective clinical trials enrolling health care workers, to assess whether BCG vaccination protects

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against Sars-CoV-2 infection or reduces its severity [11, 12]. Although the scientific data suggest a beneficial effect of BCG vaccination against Sars-CoV-2 infection and Covid-19 severity, WHO has recently reported that the currently available (April 12th) evidence is not enough to recommend BCG vaccination for the prevention of Covid-19 [13].

Local BCG chemo instillation has been widely used in uro-oncologic practice since 1976 [14]. Current Guidelines recommend the use of BCG instillation for treatment of non-muscle invasive bladder cancer (T1 high grade) or carcinoma in situ (CIS), to prevent progression and postpone radical surgical intervention [15]. The exact mechanism of the anti-tumor effect of local BCG instillation is not fully understood, but available data suggest that T_{H1} -mediated immune reaction plays a crucial role in the procedure. During the complex process of immune response, antigens are presented by MHC-II molecules resulting in activation and recruitment of granulocytes, macrophages, NK cells, CD4⁺ and CD8⁺ T-cells [5, 16, 17]. Immune-mediated cytotoxicity is derived mainly by NK cells, CD8⁺ lymphocytes, macrophages and granulocytes, while the whole process is coordinated by cytokines IL-1, IL-2, IL-6, IL-8, IL-10, TNF-alpha and IFN-gamma among others [5, 16, 17]. The reaction results in local infiltration of leukocytes in the bladder wall; however, there is evidence that BCG instillation may also induce systemic immunomodulatory effects [5, 18]. Keeping all these factors in mind, one may raise the question whether intravesically administered BCG protects against Covid-19 or reduces the virus' rate of fatal outcomes?

The TMPRSS2 and Covid-19

A recent study showed, that similar to Sars-CoV, Sars-CoV-2 needs the simultaneous presence of angiotensin converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) on the host cell's membrane to enter it [19]. The first step of this process is the attachment of Covid-19 to its receptor, ACE2 [19]. Then during the priming, the spike protein of the virus is cleaved by TMPRSS2, after which it is able to enter the host cell [19]. We have to add, that Covid-19 can use other proteases called cathepsin B and L (CatB/L) for priming, but according to the literature, TMPRSS2 is critical for viral entry into the primary target cells and viral spread in the host [19]. In line with this, camostat mesylate a clinically approved serine protease inhibitor cut the rate of viral entry into lung cells [19]. TMPRSS2 is known to be dispensable for organ function and homeostasis and is, therefore, a potential target of anti-viral therapy [19, 20]. Zhou et al. found the therapeutic effect of camostat against Sars-CoV to be promising in an *in vivo* model, hence it can be potentially effective in case of Sars-CoV-2 infection as

well [20]. Accordingly, a prospective clinical testing has just been started (NCT04321096).

TMPRSS2 is most predominantly expressed in prostatic tissue followed by the pancreas and lung epithelium [21–23]. Therefore, most of our current knowledge on TMPRSS2 is originating from prostate cancer research. The regulation of the gene is modulated by androgen, moreover it is over-expressed in prostate cancer (PCa) compared to normal prostate epithelium and is associated with tumor differentiation [22–24]. It is also known that in more than 50% of PCa cases TMPRSS2 is affected by somatic rearrangement with ERG resulting in a TMPRSS2:ERG gene fusion [25–30]. According to its androgen-dependent regulation, androgen deprivation results in lower levels of TMPRSS2 and also TMPRSS2:ERG gene expression which is restored in castration-resistant PCa [25]. All these considerations raise some interesting questions: (1) is androgen deprivation therapy able to downregulate TMPRSS2 in lung epithelial cells, and if so is it able to affect the susceptibility and/or severity of Covid-19 infection? (2) Is the known male predominance of Sars-CoV-2 infection/Covid-19 severity related to the androgen-dependent regulation of TMPRSS2 gene? (3) Does individual variability of TMPRSS2 expression (e.g. caused by polymorphism) have any impact on Sars-CoV-2 infection/Covid-19 severity?

Summary

Without a doubt, the world is facing the greatest health-care crisis of this young century to date. In the rush for a cure, governments have raised tremendous funds in attempt to address the situation. At the same time, the scientific world is cooperating and sharing its resources to expand our knowledge of the virus. The emergence and spread of Sars-CoV-2 have highlighted the importance of both basic and clinical research. Clinicians from different fields can not only help the fight against Covid-19 on the bedside, but also provide valuable data for research. As we have shown above, the field of uro-oncology offers potential for further investigation.

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