Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion

Corticosteroids for Urological Cancer Care During Coronavirus Disease 2019. Treat or Not to Treat?

Jasmin V. Waterhouse [a], James H. Hull [b], Mark Linch [a,*]

[a] Department of Oncology, University College London Cancer Institute, London, UK; [b] Department of Respiratory Medicine, Royal Brompton Hospital, Imperial College, London, UK

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a ribonucleic acid (RNA) virus first identified in Wuhan, China, in December 2019 [1]. The majority of cases present with mild symptoms; however, COVID-19 can lead to potentially lethal acute respiratory distress syndrome with hyperinflammation of the lung and cytokine release syndrome.

Official advice from the Centers for Disease and Control and Prevention (CDC) dated March 30, 2020 and from the World Health Organization (WHO) dated March 13, 2020 was to avoid corticosteroid treatments, as there are concerns that they might worsen the clinical course [1,2]. In the context of cancer care, this has led to a dilemma amongst oncologists about whether to use corticosteroids as part of anticancer regimens, supportive care, and toxicity management. Here, we outline some guidance to health care professionals to assist with a risk-benefit analysis of corticosteroid therapy for uro-oncology patients during the COVID-19 pandemic.

Case fatality rates of COVID-19 in patients with cancer was reported to be twice that of the overall fatality rate report in China (5.6% vs 2.3%; 1023 deaths in 44 672 confirmed COVID-19 patients) [3]. Oncology patients have a higher risk of severe events than noncancer patients (39% vs 8%, $p = 0.0003$), and a particular risk factor was chemotherapy treatment in the month prior to COVID-19 infection (75% vs 43%) [4]. In response to this heightened risk of fatality and severe events during cancer treatment, oncology guidelines throughout the world are being modified rapidly to reduce the burden of chemotherapy and avoid attendances at hospital.

Corticosteroids are widely used in the management of urological cancers, and are broadly given at either physiological or supraphysiological doses. Physiological doses of corticosteroids are effective as a second-line hormonal treatment for metastatic castrate-resistant prostate cancer with prostate-specific antigen response rates to 0.5 mg of dexamethasone daily of over 40% [5]. Prednisolone at 5 mg twice daily is effective at preventing the hypermineralocorticoid dose-limiting toxicity of abiraterone, a life-prolonging CYP-17,20-lyase inhibitor. Notably, in a large ($n = 1209$), randomised, double-blind study where patients with metastatic castration-sensitive prostate cancer received either abiraterone and prednisolone (give 5 mg twice daily for a median duration of 25.8 mo) or double placebo, there was no significant difference in the rate of infections between the two arms [6]. Low-dose steroids are also useful to treat cancer-associated constitutional symptoms such as anorexia, fatigue, and nausea.

Supraphysiological doses of steroids are given as an adjunct to decrease swelling (eg, preventing irreversible nerve damage in malignant spinal cord compression), and to prevent and treat cancer treatment toxicities such as docetaxel-induced capillary leak syndrome and immune checkpoint inhibitor (CPI) toxicities. CPIs, which lead to T-cell activation, have led to a step change in the management of bladder and renal cancer, but are complicated by a hyperinflammatory state requiring high-dose corticosteroids in up to 30% of cases. High-dose steroids have a number of recognised effects such as psychosis, diabetes, avascular necrosis, osteoporosis, skin fragility, and immune suppression.

An early report has suggested that cluster of differentiation (CD) 8+, CD4+, follicular helper T cells, and antibody secreting B-cells may be responsible for successful elimination of COVID-19 [7]. High-dose dexamethasone

* Corresponding author. Department of Oncology, University College London Cancer Institute, 74 Huntley Street, London WC1E6BT, UK. Tel.: +44 207 6796006.
E-mail address: m.linch@ucl.ac.uk (M. Linch).

https://doi.org/10.1016/j.eururo.2020.04.027

suppresses naïve T-cell function (both CD8+ and CD4+) [8]. While there is some in vivo evidence of B-cell depletion in the presence of short-course, high-dose steroids, primary antibody generation does not seem to be impaired [9].

The advice from the WHO and CDC to avoid corticosteroids in COVID-19 is based on concerns that viral replication might be prolonged and clearance delayed [1,2], and is largely extrapolated form the data on Middle East respiratory syndrome (MERS)-CoV and influenza. However, a more appropriate comparison is SARS-CoV-1, which is clinically and genetically closest to SARS-CoV-2 and for which corticosteroids were widely used during the 2003 SARS pandemic. Stockman et al [10] performed a systematic review of treatment effects in SARS patients. This included 29 separate studies reviewing corticosteroids comprising 21 retrospective, five prospective, one case-control, and two randomised control trials. The majority (25 studies) of studies demonstrated no convincing evidence of either benefit or detriment in clinical outcomes of patients with established SARS treated with corticosteroids [10]. The remaining studies indicated an increase in known toxicities [10].

There is currently no evidence that corticosteroid therapy in cancer patients increases the risk of infection with COVID-19 or leads to worse clinical outcomes in confirmed cases; however, supportive evidence is in its infancy. The risk of viral infections at physiological steroid doses would appear low for patients with progressive prostate cancer, and we are prescribing low-dose dexamethasone instead of palliative chemotherapy rationalising that this will be less immunosuppressive than chemotherapy and will hopefully control the disease until after the worst of the pandemic. High-dose steroids carry a theoretical susceptibility risk to COVID-19, but long-course treatments are deployed only for life-threatening complications where the need for treatment far outweighs a risk of viral susceptibility. Immune checkpoint inhibition may actually lead to improved antiviral immunity, and while we recognise the potential risks of needing high-dose steroids for toxicity, in bladder cancer we are prioritising first-line immunotherapy over chemotherapy in programmed death ligand 1 (PD-L1)-positive patients. Hyperinflammation of the lung is a fatal complication of COVID-19, and whether corticosteroids are beneficial for this is the subject of ongoing clinical trials. In a similar vein to fast-tracked respiratory expert guidelines from the National Institute of Health and Care Excellence regarding corticosteroids for their usual indications (eg, exacerbation of asthma), we are not stopping or avoiding corticosteroids for cancer indications.

It is our opinion that a risk-benefit analysis of corticosteroids should be performed for each individual patient undergoing urological cancer treatment, and it should be evaluated whether the theoretical risks associated with steroids and COVID-19 are distracting us from the clear cancer management benefits of systemic cancer therapy and corticosteroids.

Conflicts of interest: Mark Linch is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre; has received research funding from Bristol-Myers Squibb, AstraZeneca/MedImmune, Sanofi, and Astellas; and has received consulting fees from Janssen Pharmaceuticals and BioNTech. The other authors have no competing interests.

Q5

References

[1] World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. March 13, 2020. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.

[2] Centers for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). March 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.

[3] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239–42.

[4] Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21:335–7.

[5] Venkitaraman R, Lorente D, Murthy V, et al. A randomised phase 2 trial of dexamethasone versus prednisolone in castration-resistant prostate cancer. Eur Urol 2015;67:673–9.

[6] Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol 2019;20:686–700.

[7] Thevarajan I, Nguyen THO, Koutsakos M, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat Med 2020;26:453–5.

[8] Giles AJ, Hutchinson MND, Sonnemann HM, et al. Dexamethasone-induced immunosuppression: mechanisms and implications for immunotherapy. J Immunother Cancer 2018;6:51.

[9] Fan PT, Yu DT, Clements PJ, Fowlston S, Eisman J, Bluestone R. Effect of corticosteroids on the human immune response: comparison of one and three daily 1 gm intravenous pulses of methylprednisolone. J Lab Clin Med 1978;91:625–34.

[10] Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006;3:e343.

Q6

Please cite this article in press as: Waterhouse JV, et al. Corticosteroids for Urological Cancer Care During Coronavirus Disease 2019. Treat or Not to Treat? Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.04.027