Immune checkpoint inhibition in the era of COVID-19

doi: 10.1111/ced.14370

The worldwide coronavirus pandemic continues to result in significant morbidity and mortality, with almost 24 million confirmed cases to date. Approximately 80% of patients have mild disease and do not require hospitalization. A key challenge facing the medical community is predicting which patients are at risk of developing severe disease, in order to initiate early supportive treatment and to facilitate enrolment into much needed prospective clinical trials, both crucial for developing and optimizing effective treatment strategies.

Patients with cancer have already been identified as having an increased risk of developing not only COVID-19 infection, but also severe disease, both of which are associated with poorer clinical outcomes. Reassuringly, the increase in mortality from COVID-19 infection in patients with cancer may be primarily related to age, sex and comorbidities rather than to the cancer itself. Furthermore, there was no increased mortality in patients receiving and those not receiving anticancer therapy.

Nevertheless, it is at least conceivable that the type of anticancer therapy may influence the risk and course of COVID-19 infection in patients with cancer. Given the increasing use of immune checkpoint inhibition in Dermatology (metastatic melanoma, Merkel cell carcinoma and squamous cell carcinoma) we reviewed the current literature to determine the extent to which immune checkpoint inhibition has been associated with COVID-19 infection.

We performed PubMed searches to 22 June 2020 using the search terms 'COVID-19' or 'SARS-CoV-2', and ‘immune checkpoint’, ‘nivolumab’, ‘ipilimumab’, ‘pembrolizumab’, ‘avelumab’, ‘cemiplimab’ or ‘atezolizumab’. Only articles in English were included for further analysis.

We identified seven case reports and one case series of patients treated with immune checkpoint inhibitors who developed SARS-CoV-2 infections (Table 1), a total of 10 patients. An additional case of coronavirus HKU1 was reported.

Of the 10 patients with SARS-CoV-2, 30% were women and age range was 22–75 years. Half (50%) of the cases had an underlying urological tumour, 20% had metastatic melanoma, 20% had lung cancer and 10% had a haematological malignancy. Regarding treatment, 30% of the patients had received an anti-PD-L1 treatment (atezolizumab), 20% a combined anti-CTLA-4/anti-PD-1 treatment, 40% were treated with nivolumab (anti-PD-1) monotherapy and one patient (10%) received pembrolizumab (also anti-PD1). The effect of comorbidity, smoking status and ethnicity was difficult to ascertain as these were inconsistently recorded. Time from initiation of immune checkpoint inhibitor to the development of COVID-19 symptoms ranged from 48 h to > 1 year. The treatments for COVID-19 infection varied considerably, but 70% of cases received antibiotics, 20% antiviral medication and 30% received hydroxychloroquine (some patients received > 1 treatment). Three patients did not require specific therapy. The patient with coronavirus HKU1 received systemic corticosteroids for presumed checkpoint-mediated pneumonitis. In fact, the clinical and radiological presentation of immune checkpoint-related pneumonitis may be indistinguishable from that of SARS-CoV-2, making early SARS-CoV-2 PCR testing crucial. Three patients (30%) died due to coronavirus infection. Of the remaining patients, immune checkpoint therapy was recommenced or planned for four.

We found that only 10 patients with COVID-19 infection during immune checkpoint inhibition therapy have been reported. However, it is worth noting that 30% of the cases had a very mild clinical course and did not require hospitalization. Moreover, immune checkpoint therapy was safely recommenced in several patients. These points are extremely important given the fear and anxieties of patients with cancer regarding COVID-19 infection, which may lead some patients to unnecessarily delay or interrupt therapy.

Ultimately, the decision on whether to initiate and/or continue immune checkpoint therapy during the coronavirus pandemic must be based on a detailed consideration of several factors, including tumour burden and progression, comorbidities, existing immuno-suppression, palliative vs. adjuvant treatment and alternative treatment options, and cannot be generalized. Geographical coronavirus prevalence should also be considered. Irrespective of the final cancer treatment decision, the importance of facial coverings, social distancing, shielding and hand hygiene should also be emphasized.

Moving forward, there seems to be a strong case for a comprehensive and standardized prospective register of COVID infections during immune checkpoint inhibition therapy, at least at the local and national levels. This would provide vital information to determine how checkpoint inhibition influences the course of the disease.
| Author          | Age, years | Sex | Ethnicity | Comorbidities | Smoker | Cancer type | I-C treatment | Time to symptoms | Symptoms                  | CT findings                | SARS-Cov-2 | Serology                     | Correspondence |
|-----------------|------------|-----|-----------|---------------|--------|-------------|---------------|------------------|--------------------------|---------------------------|------------|----------------------------|-----------------|
| Serzan et al., 2020 | 65         | Male | Caucasian | NS            | NS     | Small cell lung cancer | Ipilimumab, nivolumab | 1 mg/kg          | Dyspnoea; yellow sputum | Ground-glass infiltrates | Positive    | IgM/IgG SARS-Cov-2 Antibodies | Clinical and Experimental Dermatology 2021 46, pp 162–194 |
| Lovly et al., 2020 | 56         | Male | NS        | Diabetes, COPD | Yes    | Renal cell carcinoma | Ipilimumab, nivolumab | 48 h             | Dyspnoea; chest pain cough | Bilateral milk glass infiltrates | Positive    |                          |                  |
| Szabados et al., 2020 | 52         | Male | NS        | NS            | No     | NS          | Nivolumab      | 2 cycles        | Fever; cough           | NS |                          |                  |
| Schmidle et al., 2020 | 68         | Male | NS        | Hypertension  | Yes    | NS          | Nivolumab      | 1 cycle        | Dyspnoea; cough             | NS |                          |                  |
| Artigas et al., 2020 | 66         | Male | NS        | Hypertension  | Yes    | NS          | Nivolumab      | 6 months       | Fever; cough; pneumonia treated with steroids | NS |                          |                  |
| Bonomi et al., 2020 | 72         | Male | NS        | Hypertension, diabetes | No | Renal cell carcinoma | Nivolumab      | 4 months      | Cough; diarrhoea; renal failure | NS |                          |                  |
| Yekediz et al., 2020 | 47         | Male | NS        | NS            | No | Renal cell carcinoma | Pembrolizumab  | 7 months      | Fatigue                | Unremarkable             | Positive    |                          |                  |
| O’Kelly et al., 2020 | 51         | Female | NS | NS            | Yes | NS          | Pembrolizumab  | 4 months      | Confusion; fever; dyspnoea; fever | Positive |                          |                  |

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| Author | Treatment | ICI treatment | Outcome | High-dose corticosteroids, tapered when swab result was positive; nivolumab monotherapy initiated | High-flow oxygen; co-amoxiclav; clarithromycin | Self-isolation | Self-isolation | Volume replacement; PIP/TAZ | Supportive | Oxygen; antibiotics | Oxygen; PIP/TAZ; doxycycline; oseltamivir; clarithromycin | Oxygen; PIP/TAZ; doxycycline; oseltamivir; ritonavir; HCQ | 
|--------|-----------|---------------|---------|-------------------------------------------------|------------------------------------------------|-------------|-------------|---------------------|-------------|---------------------|-----------------------------|-----------------------------------| 
| Serzan et al., 2020 | High-dose methylprednisolone 1 g/day (or for 2 days); prednisolone 1 mg/kg; prednisolone 2 mg/kg; infliximab 5 mg/mg; vancomycin; piperacillin/tazobactam; immunoglobulins 1 g/kg; steroids weaned; mechanical ventilation; hypoxaemic respiratory failure; PD-L1 increased in alveolar walls where viral DNA was detected; IgG response suggested infection before immunotherapy and chemotherapy | Nivolumab resumed then discontinued after CR | Alive |Alive |Alive |Alive |Alive |Alive |Not specified |Dead |NA |NA |NA |Alive | 
| Lovly et al., 2020 | | | | | | | | | | | | | | | 
| Szabados et al., 2020 | | | | | | | | | | | | | | | 
| Schmidle et al., 2020 | | | | | | | | | | | | | | | 
| Artigas et al., Bonomi et al., 2020 | | | | | | | | | | | | | | | 
| Yekediz et al., 2020 | | | | | | | | | | | | | | | 
| O’Kelly et al., 2020 | | | | | | | | | | | | | | | 

COPD, chronic obstructive pulmonary disease; CR, complete response; CT, computed tomography; CXR, chest X-ray; HKQ, hydroxychloroquine; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; IT, immunotherapy; NA, not applicable; NS, not stated; PD-L1, programmed death ligand-1; PIP/TAZ, piperacillin/tazobactam. 1. Serzan MT, Kumar PN, Atkins MB. Diffuse pneumonitis from coronavirus HKU1 on checkpoint inhibitor therapy. J Immunother Cancer 2020; 8: e000898. 2. Lovly CM, Boyd KL, Gonzalez-Ericsson PI et al. Rapidly fatal pneumonitis from immunotherapy and concurrent SARS-CoV-2 infection in a patient with newly diagnosed lung cancer. medRxiv 2020; https://doi.org/10.1101/2020.04.29.20085738; 3. Szabados B, Abu-Ghanem Y, Grant M et al. Clinical characteristics and outcome for four SARS-CoV-2-infected cancer patients treated with immune checkpoint inhibitors. Eur Urol 2020; 77: 276–80. 4. Schmidle P, Biedermann T, Posch C. COVID-19 in a melanoma patient under treatment with checkpoint-inhibitor therapy. J Immunother Cancer 2020; 8: e000986. 5. Lovly CM, Boyd KL, Gonzalez-Ericsson PI et al. Rapidly fatal pneumonitis from immunotherapy and concurrent SARS-CoV-2 infection in a patient with newly diagnosed lung cancer. medRxiv 2020; https://doi.org/10.1101/2020.04.29.20085738; 6. Bonomi L, Ghialedi L, Arnoldi E et al. A rapid fatal evolution of coronavirus disease-19 in a patient with advanced lung cancer with a long-time response to nivolumab. J Thorac Oncol 2020; 15: e8–5. 7. Yekediz E, Dursun B, Aydin GÇ et al. Clinical course of COVID-19 infection in elderly patient with melanoma on nivolumab. J Oncol Pharm Pract 2020; 26: 1289–94. 8. O’Kelly B, McGetrick P, Angelov D et al. Outcome of a patient with refractory Hodgkin lymphoma on pembrolizumab, infected with SARS-CoV-2. Br J Haematol 2020; 190: e1–3.
enabling clinicians to counsel their patients adequately. Furthermore, in light of the apparent increased mortality in various ethnic groups, combined with the potential under-reporting of ethnicity in the published COVID-19 dermatological literature, a register would ensure that key risk factors are not overlooked. In the absence of this information, it seems prudent to thoroughly assess all patients due to commence, and those currently undergoing, immune checkpoint therapy, for coronavirus risk factors and symptoms, complemented by early and rigorous SARS-CoV-2 PCR testing where clinically indicated and available.

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Conflict of interest: JK reports no conflict of interest. PT has received speaker’s honoraria from Bristol-Myers Squibb, Novartis and Roche, consultant’s honoraria from Bristol-Myers Squibb, Merck, Novartis, Sanofi and Roche, and travel support from Bristol-Myers Squibb, Pierre-Fabre and Roche. EAL has received speakers’ honoraria, travel support and/or participated in Advisory Boards for San Pharma, CureVac, BMS and Novartis.

Accepted for publication 3 July 2020

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Patient perceptions of Mohs micrographic surgery during the COVID-19 pandemic and lessons for the next outbreak

doi: 10.1111/ced.14423

Understanding patient experiences of healthcare systems during the pandemic is important to help strategize for future similar events. We operated a reduced Mohs micrographic surgery (MMS) service during the pandemic by rationalizing patients by tumour type, age, comorbidities and patient choice. We sought to establish patient expectations and concerns of attending for MMS by conducting a survey of those attending surgery over a 7-week period from 24 April 2020. The results are particularly relevant when re-establishing services in preparation for an expected upsurge of routine activity (including surgical procedures) or ‘second spike’ of COVID-19 cases later this year.

Although patients who may not have attended surgery were not surveyed, 37% of patients had at least one risk factor for COVID-19 and 27% were over the age of 70 years. Furthermore, we also had a high response rate of 96% (151 responses) reflecting an accurate representation of patient experiences.

Of the survey respondents, 52% were male and 48% female and the majority (98%) white. The age range was 30–89 years and the majority (91%) described their health status as good to excellent.

Our main findings were that the overwhelming majority of patients (82%) were relieved to have surgery. Nearly half (47%) had been worried the hospital would cancel their surgery. Only 17% considered cancelling due to concerns about contracting coronavirus, transmitting to household/family members, or taking public transport, although 54% were anxious about using public transport to attend their appointment. The overwhelming majority (80%) stated they would normally have used public transport if there was not an ongoing pandemic, but only 45% actually did.

Less than a quarter were concerned they would contract COVID-19 in hospital and 30% were concerned about transmitting to household/family members. Only 19% were concerned about the ability to social distance in hospital. Despite these concerns, patients still attended for MMS.

To our knowledge, this is the first study exploring patient perceptions of MMS during the pandemic. Patients overwhelmingly appreciated having MMS treatment in a safe environment. There were some COVID-19-related concerns; however, patients felt that attending their appointment was more important. Relatively few patients were concerned about being able to socially distance in hospital; this may reflect our strong infection-control measures and effective communication, including a nurse-led consultation prior to the appointment. During this consultation, patients were given information about