Ther Adv Med Oncol
2020, Vol. 12: 1–7
DOI: 10.1177/1758835920977002

Patients with locally advanced and metastatic cutaneous squamous cell carcinoma treated with immunotherapy in the era of COVID-19: stop or go? Data from five Italian referral cancer centers

Maristella Saponara, Laura Pala, Fabio Conforti, Marco Rubatto, Ivana De Risi, Francesco Spagnolo, Michele Guida, Paolo Bossi, Pietro Quaglino and Paola Queirolo

Correspondence to:
Maristella Saponara
Division of Medical Oncology for Melanoma, Sarcoma, and Rare Tumors, IEO, European Institute of Oncology IRCCS, Milan, Italy
maristella.saponara@ieo.it

Laura Pala
Fabio Conforti
Division of Medical Oncology for Melanoma, Sarcoma, and Rare Tumors, IEO, European Institute of Oncology IRCCS, Milan, Italy

Marco Rubatto
Department of Medical Sciences, Dermatology Clinic, University of Turin, Turin, Italy

Ivana De Risi
Medical Oncology Department, IRCCS Istituto dei Tumori "Giovanni Paolo II", IRCCS, Bari, Italy

Francesco Spagnolo
Department of Medical Oncology, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

Michele Guida
Medical Oncology Department, IRCCS Istituto dei Tumori "Giovanni Paolo II", IRCCS, Bari, Italy

Paolo Bossi
Department of Medical and Surgical Specialties, Radiological Sciences and Public Health - Medical Oncology, ASST-Spedali Civili, University of Brescia, Brescia, Italy

Pietro Quaglino
Department of Medical Sciences, Dermatology Clinic, University of Turin, Turin, Italy

Paola Queirolo
Division of Medical Oncology for Melanoma, Sarcoma, and Rare Tumors, IEO, European Institute of Oncology IRCCS, Milan, Italy

***Abstract*:** Since the end of 2019, global healthcare systems have been dealing with the COVID-19 pandemic.

In oncology, the biggest questions concern interaction of COVID-19 with pre-existing cancer disease and with systemic anticancer treatments. With regards to immunotherapy, there is uncertainty about its effect in the context of COVID-19 in terms of probability and course of viral infection.

Herein, we retrospectively report data of patients with advanced cutaneous squamous cell carcinoma (cSCC) treated with immunotherapy at five Italian referral cancer centers during the pandemic. cSCC is a disease poorly represented in the literature, typically affecting fragile, elderly patients, with multiple comorbidities and often immunosuppressed. Overall, 54 patients were identified, most of them coming from Lombardy and Piedmont, the two regions hit hardest by COVID in Italy. In most cases, our choice was to continue treatment, reserving temporary interruptions only to patients considered particularly at risk for age and comorbidity. A total of 9% of patients developed new-onset symptoms or had chest radiological assessment potentially related to COVID-19. Nasopharyngeal swabs were collected in all suspicious cases and two hospitalized patients were found to be positive. In conclusion, the outbreak of COVID-19 is a major worldwide health concern. Our data indicate that COVID-19 mortality in patients with cancer may be principally driven by advancing age, the presence of other comorbidities, and other cancer-related conditions (i.e. hospitalization). Our data further suggests the safety of continued use of PD-1 blockade during the COVID-19 pandemic (obviously implementing all the safety measures in the hospital environment) also considering the possible negative effects of a prolonged suspension on the course of the tumor evolution. We think it is useful to collect and report case studies coming from reference centers, because they can represent helpful examples for the scientific community of clinical management of patients affected by cancer in this difficult period and guide further research.

Keywords: Anti-PD-1, COVID-19, cSCC, cutaneous squamous cell carcinoma, immunotherapy

Received: 10 August 2020; revised manuscript accepted: 9 November 2020.

Introduction

Since the end of 2019, global healthcare systems have been dealing with the coronavirus disease 2019 (COVID-19) pandemic, a disease caused by SARS-CoV-2 infection that started in China and then spread worldwide. COVID-19 has severely shaken the global social, economic, and, most of all, health systems. The number of people

affected by the pandemic is huge, with more than 17 million people infected and over 650,000 dead worldwide as of 1 August 2020.[1]

This situation represents and will remain an absolute challenge for all clinicians.

In particular, in oncology, the interaction of COVID-19 with pre-existing cancer disease and with systemic anticancer treatments is of special interest. Some initial retrospective and small case studies suggested that patients with cancer and receiving systemic drugs are at a higher risk of infection and its sequelae than their counterparts without cancer or who are not receiving anticancer treatment.[2–4]

More recently, experiences with more cases have become available, but report conflicting results.[5,6] In any case, most of the publications refer to patients treated with chemotherapy. The biggest questions concerning cancer patient management during the COVID-19 pandemic remain as follows. Who is at specific risk? Are there any treatment decision recommendations? Is it possible to draw up a list to identify priority cancer patients? Is there a certain heterogeneity between the different tumor subtypes or anticancer therapies and the rooting and course of COVID?

In order to update the information available and try to find answers to these questions, we think it is useful to collect and report case studies coming from reference centers for specific tumors. In fact, they can represent helpful examples for the scientific community in the clinical management of patients affected by cancer in this difficult period and to guide further research.

Herein, we retrospectively report data of patients with advanced cutaneous squamous cell carcinoma (cSCC) treated with immunotherapy at five Italian referral cancer centers for melanoma and other skin cancers: Istituto Europeo di Oncologia (IEO) in Milan, Città della Salute e della Scienza University-Hospital in Turin, IRCCS "Giovanni Paolo II" in Bari, IRCCS San Martino Hospital in Genoa, and Spedali Civili in Brescia.

In this period of emergency medicine, ethics committees have been convened with virtual meetings only for urgent matters. For institutions that required consent, when possible, patients' written informed consent was obtained. A waiver was allowed for those who were not able to sign. All study procedures were in accordance with the precepts of good clinical practice and the Declaration of Helsinki. Moreover, the following requirements regarding personal data were guaranteed: anonymization, encryption of the database, confidentiality, integrity and resilience of treatment systems and services, with strict control on access to data.

Case reports

We included all patients who completed at least one cycle of immunotherapy during the outbreak of the pandemic in Italy, from 21 February to 30 April 2020.

Considering that immunotherapy with cemiplimab for cSCC in Italy is currently approved only for the treatment of advanced forms, all cases described here concern patients with active disease and no adjuvant therapy. The series also includes 10 patients enrolled in the I-Tackle clinical trial.[7] Similarly, these are patients with locally advanced or metastatic disease, not amenable to surgical or radiotherapy treatment, who received immunotherapy with pembrolizumab with or without cetuximab.

Overall, 54 patients with locally advanced (59%) or metastatic (41%) cSCC and treated with immunotherapy were identified (Table 1). Thirty-six (67%) were men and the median age was 80 years (range 55–95).

Most of the patients came from Lombardy and Piedmont, the two regions hit hardest by COVID in Italy.

Almost all patients (91%) had comorbidities. The most frequent was hypertension, but in more than half of cases (57%) there were two or more concomitant pathologies, including past solid tumors, hematological malignancies, and acquired immune deficiency syndrome. A total of 45 (83%) patients were pretreated or heavily pretreated with repeated surgery, radiotherapy, chemotherapy, or combinations of these treatments.

During the evaluation period, a total of 31 patients (57%) continued treatment without interruption or delay and six patients interrupted for disease progression or causes other than related to COVID. However, 17 patients (31%) had a treatment delay/interruption due to COVID

Table 1. Characteristics of patients.

Sex		
Male	36	67%
Female	18	33%
Age (years), median (range)	80	55–95
Region		
Lombardy	16	30%
Piedmont	14	26%
Others	24	44%
Cancer stage		
Locally advanced	32	59%
Metastatic	22	41%
Comorbidities		
Hypertension	33	
Other cardiovascular disease	19	
Chronic obstructive pulmonary disease	2	
Diabetes	8	
Immunosuppression	3	
Others	29	
Previous treatment		
Surgery	18	33%
Surgery + radiotherapy	21	39%
Surgery + chemotherapy	4	7%
Surgery + radiotherapy + chemotherapy	2	4%
No previous treatment	9	17%
Current immunotherapy (type)		
Cemiplimab	44	81%
Pembrolizumab	10	19%
Clinical trials		
Yes	10	19%
No	44	81%
Treatment delay/interruption		
Yes, due to COVID-19	17	31%
Yes, due to other causes	6	11%
No	31	57%
Length of treatment delay (weeks), median (range)	3	1–11
Onset of suspicious symptoms/chest radiological images	5	9%
SARS-CoV-2 swab in suspected cases		
Positive	2	
Negative	3	

emergency. The median length of treatment delay was 3 weeks, equivalent to one cycle of therapy, with a range of 1–11 weeks. The discontinuation rates in the clinical study population were lower, probably because of the typical selection of patients included in clinical trials (overall better performance status) and to the mandatory schedule of visits.

The main reason leading to treatment delay was the perception of an increased risk of infection for patients with older age or severe comorbidities. However, delayed patients were periodically contacted by phone to assess health status and onset of new symptoms.

During the study period, five (9%) patients developed new-onset symptoms potentially related to COVID-19, including fever, cough, and dyspnea and/or had chest radiological assessment positive or doubtful for infection by coronavirus.

Nasopharyngeal swabs were collected in all of such clinical and/or radiological strongly suspicious cases and two patients were found positive for SARS-CoV-2.

The first patient, a 92-year-old man, received cemiplimab since January 2020 for a locally advanced cSCC of the scalp. After two cycles of therapy, during the pandemic peak in Italy, he was hospitalized for mild asthenia in Liguria against the advice of his doctors and on request of his caregivers. During hospitalization, the patient's roommate was found positive for

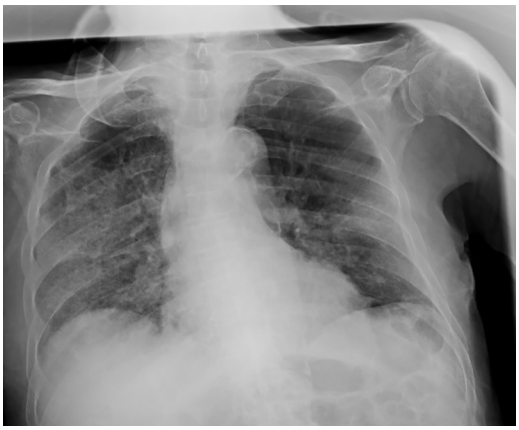

Figure 1. Chest X-ray of a 92-year-old man hospitalized for asthenia during treatment with cemiplimab for cSCC of the scalp. One month later, he experienced clinical worsening and fever and chest X-ray showed diffuse reticulonodular-looking opacities in the middle-basal right field of plausible interstitial nature. A similar, but less-extensive finding is also appreciable on the left.

COVID-19, afterwards he also developed fever and chest X-ray was compatible with COVID-19 interstitial pneumonia (Figure 1).

The second was a 77-year-old woman affected by locally advanced cSCC of the perigenital/anal region on therapy with cemiplimab since December 2019 and previously treated with surgery and radiotherapy. She had post-traumatic paraplegia and iron deficiency anemia. After four cycles of therapy, with worsening anemia, she was admitted to a peripheral hospital in Piedmont, the second most affected region of Italy, and started iron replacement therapy. During hospitalization, she developed fever and dyspnea and CT scan showed bilateral pulmonary interstitial involvement.

In both cases, the nasal swab confirmed the diagnosis of COVID-19 and unfortunately the two patients died afterwards from lung complications.

Of the three patients with symptoms and negative for SARS-Cov-2, none died. The reason for the clinical findings in these strongly suspicious cases was autoimmune toxicity. In particular, two patients developed interstitial pneumonia and one patient developed fever requiring steroids, during the time period. The interstitial pneumonia recovered without sequela and the patients resumed immunotherapy after skipping only one dose. They then obtained very good tumor control, whereas the patient with fever who skipped two doses unfortunately then experienced clinical worsening due to disease progression.

Certainly, in other times, the recognition of these side effects would have been easier, but in the COVID era the similarity between the symptoms of immunotherapy and those of the infection necessarily required greater caution in ascribing and managing such symptoms.

Discussion

The outbreak of COVID-19 pandemic is a major worldwide health concern. Patients with cancer seem to have a higher risk of contracting the infection and to have a worse course of the disease. The reasons can be many, including: advanced age (50% of cancer patients are >70 years of age[8]); frequent visits to hospitals to receive treatments and a subsequent high risk of COVID-19 transmission between patients, infusion staff and medical system; their immunosuppressive status determined by the tumor itself and by anticancer treatments such as chemotherapy and radiotherapy.

With regards to immunotherapy, there is uncertainty about its effect in the context of COVID-19 in terms of probability of infection and course of viral infection. On one side, PD-1 blockade might be harmful by increasing the hyperactive immune phase of COVID-19, on the other, it could theoretically improve outcomes, enhancing immunologic control of viral infections.[9]

Other considerations regarding immunotherapy and COVID-19 are: (i) the diagnostic dilemma, as symptoms of COVID-19 can mimic adverse events related to immunotherapy; radiographical appearance of COVID-19 and immunotherapy pneumonitis may be similar and include diffuse and bilateral ground-glass opacities, thus distinguishing between viral pneumonia and lung toxicity to immunotherapy could be very difficult; (ii) the management of autoimmune toxicity, often requiring steroid-based therapy, which is a concern for increased risk in the clinical course of COVID-19.

This year, data from two studies aimed at evaluating the interaction between COVID-19 and cancer were presented at ASCO 2020 and recently published *in extenso*.

The first is an American study (CCC19) of about 1000 patients affected by solid and hematological tumors. The second is an Italian designed study (TERAVOLT), which then involved cases from countries worldwide, of 400 thoracic cancer patients. The results of these studies represent an important international effort to define the COVID-19/cancer relationship.[10,11]

The mortality rates reported were 13% and 35.5%, respectively, defining the main risk factors for death as: advanced age, presence of comorbidity, and poor performance status. The higher mortality rate in the TERAVOLT study could be also influenced by low admission rates in intensive care units (ICUs) at the peak of the pandemic for these patients (being the priority criteria for ICU admission aimed at guaranteeing intensive treatment to patients with greater chances of therapeutic success). Other factors that appear to increase mortality risk are: concomitant therapy with steroids, anticoagulants, and chemotherapy. Treatment with target therapy or immunotherapy did not seem associated with increased risk of death. In the TERAVOLT study, when looking at patients who had died, 46.8% were on chemotherapy, 22% on immunotherapy, 12.8% on target therapy, and 9.2% on radiotherapy.

These and other numerous case series of patients suffering from other tumors are showing that the risk of death by infection is particularly high in patients with lung cancer during standard chemotherapy treatment and a likely contributor is the presence of cofactors such as pre-existing lung disease, impaired respiratory function, smoking habit, etc.[12–14]

To the best of the authors' knowledge, our report, though encompassing a small series of patients observed retrospectively, shows for the first time the management of patients affected by locally advanced and metastatic cSCC in the era of COVID-19. This is a disease poorly represented in the literature, typically affecting fragile patients, as they are often elderly, with multiple comorbidities, and often immunosuppressed. Our data support the hypothesis that immunotherapy does not necessarily represent a risk factor for COVID-19 infection.

In most cases, our choice, based on a risk–benefit analysis, was to continue treatment, complying with schedules, reserving temporary interruptions only to patients considered particularly at risk for age and comorbidity. Available data regarding continuation versus interruption of immunotherapy show that maintenance of dose intensity with immunotherapy could be less relevant as with chemotherapy (because activation of the immune response is generally maintained after treatment discontinuation). However, this is particularly true for patients who obtained complete response during treatment.[15] As all the cases reported here referred to patients with advanced disease, often disfiguring, at risk of complications and painful symptoms, the primary goal was not to risk losing control of the disease as obtained before the spread of the COVID-19 pandemic.

During the observation period in which the study was conducted, no particular complications related to the discontinuation of therapy were observed. However, we are starting to witness the feared negative effects of suspension or delay of treatment during the pandemic and this applies not only to postponements of surgical programs and cycles of systemic therapy, but also to delay of follow-up visits and cancer screening programs.

The 2 out of 54 patients who tested positive for COVID-19 were an elderly man (92 years old) and a 77-year-old woman with important comorbidities. Both were hospitalized for reasons other than infection and then became symptomatic for COVID-19, which does not allow us to exclude that the infection was due to hospitalization in long-term hospital facilities.

In most cases, the main challenge in patients' management has been the appearance of confounding symptoms or signs during immunotherapy, which could be either adverse events of immunotherapy or COVID-19 contagion (fever, dyspnea, diffuse areas of ground-glass at CT scan) (Figure 2).

In all cases suspect of infection, the nasopharyngeal swab was performed, allowing diagnosis to be excluded or confirmed and proper therapies to be started.

In conclusion, our data indicate that COVID-19 mortality in patients with cancer may be principally driven by advancing age, the presence of other comorbidities, and other cancer-related

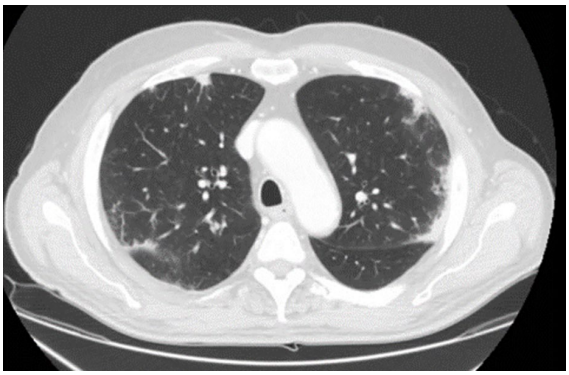

Figure 2. CT scan of 73-year-old man performed during treatment with cemiplimab showing diffuse and bilateral areas of ground-glass compatible with interstitial pneumonia, in the absence of symptoms. Nasopharyngeal swab excluded COVID-infection.

conditions (i.e. hospitalization). Our data further suggests the safety of continued use of PD-1 blockade during the COVID-19 pandemic also considering the possible negative effects of a prolonged suspension on the course of the tumor evolution, meeting the expectations and needs of patients.

Obviously, this can be pursued only by implementing all safety measures in the hospital environment. It will be necessary to perform triage at each access, verify the proper use of adequate personal protective equipment by patients, maintain social safety distances, and make hand sanitizer gel available in every office/waiting room/infusion room.

Other practical recommendations to minimize risks associated with the regular carrying out of treatment programs are:

(i) perform laboratory tests in centers closer to the patient's home;
(ii) have the lab test results 24 h before the infusion in order to prescribe/prepare in advance therapies and avoid long waits and stays of patients in hospital;
(iii) allow only the patient (only one relative if strictly necessary) to enter the hospital, avoiding gatherings in the waiting rooms.

Further follow-up and expanded sample sizes are needed to fully assess long-term safety and reliability of our observations and to further determine how PD-1 blockade may affect susceptibility to COVID-19.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Maristella Saponara https://orcid.org/0000-0003-0715-171X

Ivana De Risi https://orcid.org/0000-0002-6330-797X

References

1. Ministero della Salute. COVID-19 - situazione nel mondo, http://www.salute.gov.it (accessed 1 August 2020).
2. Dai M, Liu D, Liu M, *et al*. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. *Cancer Discov* 2020; 10: 783–791.
3. Liang W, Guan W, Chen R, *et al*. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; 21: 335–337.
4. Yu J, Ouyang W, Chua MLK, *et al*. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol*. Epub ahead of print 25 March 2020. DOI: 10.1001/jamaoncol.2020.0980.
5. Lee LYW, Cazier JB, Starkey T, *et al*; UK Coronavirus Cancer Monitoring Project Team. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet*. Epub ahead of print 28 May 2020. DOI: 10.1016/S0140-6736(20)31173-9.
6. Tian J, Yuan X, Xiao J, *et al*. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. *Lancet Oncol*. Epub ahead of print 29 May 2020. DOI: 10.1016/S1470-2045(20)30309-0.
7. ClinicalTrials.gov. Immunotherapy +/– EGFR inhibitor in advanced/metastatic cSCC: tackling primary and secondary resistance (I-Tackle), https://clinicaltrials.gov/ct2/show/NCT03666325

8. Associazione Italiana Oncologia Medica. I numeri del cancro in Italia 2018: incidenza, mortalità e sopravvivenza per tumore in Italia, https://www.aiom.it/wp-content/uploads/2018/08/20180927RM_01_Gori.pdf
9. Bersanelli M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. *Immunotherapy* 2020; 12: 269–273.
10. Warner JL, Rubinstein S, Grivas P, *et al. Clinical impact of COVID-19 on patients with cancer: Data from the COVID-19 and Cancer Consortium (CCC19)*. Presented at American Society of Clinical Oncology (ASCO): cancer care in the time of COVID: assessing impact and future directions, 29–31 May 2020. Abstract LBA110.
11. Horn L, Whisenant JG, Torri V, *et al. Thoracic Cancers International COVID-19 Collaboration (TERAVOLT): impact of type of cancer therapy and COVID therapy on survival*. Presented at American Society of Clinical Oncology (ASCO). Cancer care in the time of COVID: assessing impact and future directions, 2020. Abstract LBA111.
12. Kuderer NM, Choueiri TK, Shah DP, *et al*. COVID-19 and Cancer Consortium. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet* 2020; 395: 1907–1918.
13. Luo J, Rizvi H, Egger JV, *et al*. Impact of PD-1 blockade on severity of COVID-19 in patients with lung cancers. *Cancer Discov*. Epub ahead of print 12 May 2020. DOI: 10.1158/2159-8290. CD-20-0596.
14. Garassino MC, Whisenant JG, Huang LC, *et al*. TERAVOLT investigators. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. *Lancet Oncol* 2020; 21: 914–922.
15. Robert C, Ribas A, Hamid O, *et al*. Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. *J Clin Oncol* 2018; 36: 1668–1674.