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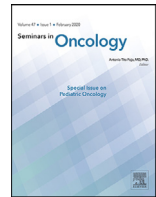
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Data of Italian Cancer Centers from two regions with high incidence of SARS CoV-2 infection provide evidence for the successful management of patients with locally advanced and metastatic melanoma treated with immunotherapy in the era of COVID-19

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ABSTRACT

Background: Patients with cancer are presumed to have a higher risk to contract SARS-CoV-2 infection, because of their immunosuppressed status. The impact and course of COVID-19 infection in cancer patients receiving immunotherapy remains unknown.

Objectives: To evaluate the safety of the management of patients with advanced melanoma treated with immunotherapy in 2 Cancer Centers located in areas of Italy with a high incidence of COVID-19 infections.

Methods: We retrospectively analyzed data from January 1 to April 30, 2020 on patients with locally advanced and metastatic melanoma receiving immunotherapy at either Istituto Europeo di Oncologia or Città della Salute e della Scienza University Hospital.

Results: One-hundred and sixty-nine patients with stage III and IV melanoma were treated with an immunotherapy regimen at either Istituto Europeo di Oncologia or Città della Salute e della Scienza University Hospital. One-hundred and four patients continued treatment without interruption or delay, while 49 patients had a treatment delay. The main reasons for treatment delay were older age (median age of the group of patients with or without treatment-delay, respectively 60 and 69 years, P value <0.001) and/or presence of comorbidities (percentage of patients with at least one comorbidity respectively 81% and 62%, in patients with or without treatment delay, P value = 0.001). One-hundred and twelve patients had at least 1 thoracic CT scan performed and radiological findings suspicious for COVID-19 were observed in only 7 cases (4%). Fifteen patients (9%) developed symptoms potentially related to COVID-19; nasopharyngeal swabs were collected in 9 patients and only 1 was positive for SARS-CoV-2.

Conclusions: The incidence of symptomatic COVID-19 infection observed in our cohort of patients with advanced malignant melanoma treated with immunotherapy appears meaningfully lower as compared with that reported in the overall population in Italy as well as in patients affected by solid tumors. We conclude that in patients with locally advanced and metastatic melanoma, immunotherapy can be safely continued without delay in the majority of cases, reserving precautionary delay only for the most frail patients.

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Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome Coronavirus 2.

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Table 1

- Clinical and epidemiological features of patients with melanoma treated at Istituto Europeo di Oncologia and Città della Salute e della Scienza University Hospi

Patients n (%)		169 (100%)
Sex	Male	102 (60%)
	Female	67 (40%)
Median age	N (range)	62 (21–89)
Stage:	III	64 (38%) 105 (62%)
	IV	<ul style="list-style-type: none"> • M1a 18 (17%) • M1b 31 (30%) • M1c 35 (33%) • M1d 21 (20%)
Setting of treatment	Neoadjuvant	6 (4%)
	Adjuvant	61 (36%)
	Metastatic/palliative	102 (60%)
Region of residence	Lombardy (L)	47 (28%)
	Piedmont (P)	90 (53%)
	Northern regions other than L and P	7 (4%)
	Central regions	9 (5%)
	Southern regions	15 (9%)
	Out of Italy	1 (1%)
Comorbidities	None	54 (32%)
	At least 1	115 (68%)
Smoking status	Never	85 (51%)
	Former	36 (21%)
	Current	12 (7%)
	Not reported	36 (21%)
Therapy	Anti PD-1	142 (84%)
	Anti CTLA-4	4 (2%)
	Anti PD-1 + Anti CTLA-4	6 (4%)
	Anti PD-1 ± antivascular	7 (4%)
	Anti PD-1 ± T-VEC	1 (0.7%)
	Anti PD-L1 + Anti BRAF + Anti MEK	7 (4%)
	Anti PD-1 + NTKR-214	2 (1.3%)
Treatment on a clinical trial		33 (20%)
Receiving standard therapy		136 (80%)
Symptoms	Yes	15 (9%)
	No	154 (91%)
Nasopharyngeal swabs		7 (4%)
CT scan performed	Performed	112 (66%)
	Not performed	57 (34%)
Suspect radiologic findings		7 (4%)
Treatment delay	Yes	49 (29%)
	No	104 (62%)
Treatment discontinuation		16 (9%)
		<ul style="list-style-type: none"> • PD: 8 (50%) • End of treatment: 3 (19%) • Toxicity: 2 (12%) • Not reported: 3 (19%)

Notes: L: Lombardy; NKTR-214: Bempegaldesleukin; P: Piedmont; PD: progressive disease; PD-1: programmed cell death protein 1; PD-L1: programmed cell death protein ligand 1; T-VEC: Talimogene laherparepvec.

The COVID-19 pandemic has emerged as a major worldwide health concern, with millions of people infected and hundreds of thousands dead. As of July 2020, Italy still ranks as one of the countries with the highest incidence of COVID-19 in the world [1]. The Lombardy and Piedmont regions account for over 50% of total cases and over 60% of deaths for COVID-19 infection in the country [2].

Because of their immunosuppressed status conferred by either the tumor itself or by anticancer treatments, including chemotherapy and radiotherapy, patients with cancer are generally thought to have a higher risk of developing infectious complications [3]. However, the impact and course of viral infection in cancer patients receiving immunotherapy remains largely unknown. Thus, we retrospectively collected and analyzed data on patients with a diagnosis of melanoma who were treated with immunotherapy from January 1 to April 30, 2020 at 2 Italian Cancer Centers, Istituto Europeo di Oncologia and Città della Salute e della Scienza University Hospital, located respectively in Milan (Lombardy) and Turin (Piedmont).

In total 169 patients with a diagnosis of either stage III or stage IV melanoma undergoing treatment with an immunotherapy con-

taining regimen presented to the outpatient clinics of the Istituto Europeo di Oncologia or the Città della Salute e della Scienza University Hospital. Table 1 summarizes the clinical and epidemiological features of patients evaluated. No differences were found between the Lombardy and the Piedmont data. Sixty-four (38%) patients had a surgically resected, stage III melanoma, and 105 (62%) had stage IV disease. Eight out of 105 had an oligometastatic disease: 7 had undergone surgical resection and received adjuvant treatment, while 1 received neo-adjuvant therapy. One-hundred and two (60%) were males, and the median age was 62 years (range 21–89). Most came from the northern regions of Italy, particularly Lombardy (47; 28%) and Piedmont (90; 53%). The majority of patients had at least 1 comorbidity (115; 68%), and between them 48 (41%) suffered from multiple comorbidities. Forty-eight out of 169 patients (28%) were former or current smokers. Most patients (136; 80%) were treated with standard immunotherapies, while 33 (20%) received treatments within a clinical trial.

In most of cases, patients received an anti-PD1 (142; 84%) or anti-CTLA4 (4; 2%) drug as monotherapy; the other regimens administered included an anti-PD-1/PDL-1 in combination with

anti-CTLA-4 (6; 4%), anti-vascular/placebo (7; 4%), TVEC/placebo (1; 0.7%), anti BRAF plus anti-MEK (7; 4%) or NKTR-214 (2; 1.3%). During the time period evaluated, a total of 104 patients continued treatment without interruption or delay with respect to the planned schedule, 16 patients interrupted treatments for progressive disease or end of treatment, and 49 patients (29%) had a treatment delay, a fraction that was slightly higher than the 15% of delays observed during the 4 months before the COVID-19 pandemic started.

The median length of treatment delay was 4 weeks, ranging from 3 to 9 weeks. In about half of cases, the reason leading to treatment delay was to avoid hospital admission of patients at higher risk for COVID-19, such as those who were older - the median age of the group of patients with or without treatment-delay, was respectively 60 versus 69 years, P value <0.001) and/or had comorbidities - the percentage of patients with at least 1 comorbidity was respectively 81% and 62%, in patients with or without treatment delay, P value = 0.001). All patients whose treatment administration was delayed, had been on therapy for at least 4 months before delay and their disease was felt to be under control.

All patients evaluated, had access to 1 of the 2 centers or were contacted by phone to assess their health status and query regarding the onset of new symptoms in the prior 2 weeks. During the study period, only 15 patients (9%) developed new-onset symptoms potentially related to COVID-19, including fever, cough, dyspnea, anosmia, dysgeusia, or diarrhea.

A total of 112 patients had at least 1 thoracic CT scan performed as follow-up of their oncologic disease, and radiological findings suspicious for COVID-19 were observed only in 7 cases (4%). Nasopharyngeal swabs were collected in 9 patients with clinical and/or suspicious radiologic findings, and only 1 was positive for SARS-CoV2. The latter patient, a 55 years old male, without comorbidities, had been receiving pembrolizumab for 2 years and had achieved a complete response. He experienced a paucisymptomatic COVID-19 infection, with moderate fever and anosmia lasting 4 days, and a mild bilateral pulmonary interstitial involvement highlighted on radiologic scans. Therapy with hydroxychloroquine and azithromycin was administered, with swabs negative for SARS-CoV-2 after 1 month.

The incidence of symptomatic COVID-19 infection observed in our cohort of patients, appears meaningfully lower as compared with that reported in the overall population in Italy as well as in patients affected by solid tumors [4]. This supports the thesis that in patients with locally advanced and metastatic melanoma, immunotherapy can be continued safely without interruptions or delays in the majority of cases, reserving precautionary delay only in the most frail patients identified on the basis of older age and/or comorbidities. A weakness of our data, was the low number of nasopharyngeal swabs performed, that do not allow us to estimate the percentage of patients with asymptomatic COVID-19 infections. However, a relevant negative predictive value for COVID-19 infec-

tion has been reported for thoracic CT scan and 66% of our patients had a CT scan of the chest performed during the period of observation, as part of their oncologic care [5]. Indeed, a large number of our patients underwent thoracic CT scan for staging purposes, and only 7 of the 112 patients had radiological findings compatible with COVID-19 infection, and in only 1 was COVID-19 infection confirmed by swab. These data, seem also support a low percentage of asymptomatic COVID-19 infection in our cohort of patients.

The debate as to whether patients with a diagnosis of cancer treated with immunotherapy have a higher risk of contracting COVID-19 infection as well as develop more symptomatic and complicated forms of disease continues. Our data argue against these hypotheses and highlight the urgent need to better explore this issue, considering the potential clinical implications.

Authors' Contribution

Conceptualization: Laura Pala, Fabio Conforti, Paola Queirolo; Methodology: All authors; Software; Validation: Not applicable; Formal analysis: Laura Pala, Fabio Conforti; Investigation: All authors; Resources: All Authors; Data Curation Writing - Original Draft : Laura Pala, Fabio Conforti; Writing - Review & Editing: All authors; Visualization: All Authors; Supervision: All authors; Project administration: All authors; Funding acquisition: not applicable.

Conflict of Interest

Paola Queirolo has received lecture fees from and served on the advisory board for Roche, Novartis, Bristol-Myers Squibb, Merck, Sharp & Dohme, Amgen. All other authors have declared no conflict of interest.

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