SARS-CoV-2 infection and adverse events in patients with cancer receiving immune checkpoint inhibitors: an observational prospective study

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ABSTRACT

Background In ambulatory patients with cancer with asymptomatic or pauci-symptomatic SARS-CoV-2 infection, the safety of targeted therapies (TTs), chemotherapy (CT) or immune checkpoint inhibitors (ICIs) therapy is still unknown.

Material and methods From the start of the first epidemic wave of SARS-CoV-2 in Bergamo, Italy, we have prospectively screened all consecutive outpatients who presented for treatment to the Oncology Division of the Papa Giovanni XXIII Hospital, Bergamo for SARS-CoV-2 antigen expression. We identified patients treated with ICIs and compared these to patients with the same cancer subtypes treated with TTs or CT.

Results Between March 5 and May 18, 293 consecutive patients (49% melanoma, 34% non-small cell lung cancer, 9% renal cell carcinoma, 8% other) were included in this study: 159 (54%), 50 (17%) and 84 (29%) received ICIs, CT or TTs, respectively. Overall 89 patients (30.0%) were SARS-CoV-2 positive. Mortality of SARS-CoV-2-positive patients was statistically significantly higher compared with SARS-CoV-2 negative patients (8/89 vs 3/204, respectively, Fisher's exact test $p=0.004$). All deaths were due to COVID-19. Serious adverse events (SAEs) were more frequent in SARS-CoV-2-positive patients compared with SARS-CoV-2-negative cases (Cochran-Mantel-Haenszel (CMH) test $p=0.0008$). The incidence of SAEs in SARS-CoV-2 positive compared with SARS-CoV-2 negative patients was similar in ICI and CT patients (17.3% and 3.7% for positive and negative patients in ICIs and 15.4% and 2.7% in CT, Breslow-Day test $p=0.891$). No COVID-19-related SAEs were observed in the TTs patients.

Conclusions The incidence of SAEs was higher for SARS-CoV-2-positive patients treated with ICIs and CT, mostly in advanced disease. No SAEs were observed in patients treated with TTs. SAEs were COVID-19 related rather than treatment related. Treatment with ICIs does not appear to significantly increase risk of SAEs compared with CT. This information should be considered when determining treatment options for patients.

INTRODUCTION

The recent global outbreak of SARS-CoV-2 infection and the resulting COVID-19 poses

an unprecedented health crisis that was declared a pandemic by the WHO on March 11, 2020.¹ The causative pathogen has been identified as a beta-coronavirus with high sequence homology to bat coronaviruses.² This virus uses ACE2 receptor as the dominant mechanism of cell entry.³ The considerable spread of the current pandemic has brought tremendous pressure and disastrous consequences for public health and medical systems worldwide.

Although mild respiratory tract infection characterizes most COVID-19 cases, a serious and potentially fatal illness can occur, principally driven by a respiratory distress syndrome and/or vascular complications.⁴ Severe outcomes are more common in older male patients with secondary comorbidities. Hypertension, chronic respiratory system diseases, diabetes and cardiac diseases were highlighted as potential risk factors for poor outcomes from COVID-19. Serum analysis showed higher plasma levels of proinflammatory cytokines in severely ill patients.⁴ Since chronic diseases may lead to low immune function, a strong correlation between the host immune status and COVID-19 prognosis has been highlighted. Therefore, immune-suppressed patients were added within the higher-risk group for severe illness from COVID-19.

Recently, studies on outcome of patients with cancer with COVID-19 disease have been reported^{5–7} and they suggest that risk of death is associated with advancing patient age, male gender and comorbidities, similarly to patients without cancer. However, it remains unclear whether the use of anticancer treatment impacts on outcomes for patients who are positive for SARS-CoV-2.

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Checkpoint inhibitors have revolutionized the outcomes for many different cancers and treatments based on programmed cell death protein 1 (PD-1) inhibition are the standard of care in many common and rare tumor types. Treatment-related toxicities with immune checkpoint inhibitors (ICIs) are common and due to recognition of autoantigens by the immune system, resulting in immune toxicity. The potential impact of treating patients with asymptomatic or pauci-symptomatic SARS-CoV-2 infection with ICIs is still unknown. Currently, little is known about specific phenotypic and/or functional T cell changes associated with symptomatic and asymptomatic SARS-CoV-2 infection. Early studies consistently showed an increased presence of activated T cells, primarily characterized by expression of HLA-DR, CD38, CD69, CD25, CD44, and Ki-67.^{8–10} Furthermore, levels of PD-1 seem to increase in circulating T cells. PD-1 expression is commonly associated with T cell exhaustion, but it is also well known that, in the context of acute viral infections, PD-1 is also expressed by activated effector T cells during early phases of T cell priming. Building on this biological background, two potential clinical scenarios can be hypothesized: (1) ICIs treatment may help to counteract the immunologic impairment of T cells induced by COVID-19 infection, contributing to viral clearance through the reactivation of PD-1⁺ viral epitope-specific T cells; (2) ICIs therapies can conversely shift COVID-19 disease towards its more aggressive inflammatory stage through the promotion of different immune activation mechanisms.

The city of Bergamo was the epicenter of the recent Italian SARS-CoV-2 infection outbreak. The tragic SARS-CoV-2 emergency did not spare patients with cancer and further complicated their management. Considering the lack of clinical data in the current literature, we therefore prospectively evaluated whether, and to what extent, the asymptomatic or pauci-asymptomatic SARS-CoV-2 infection increased the burden of toxicities in patients treated with ICIs in the ambulatory setting, and compared these rates with patients treated with chemotherapy (CT) and targeted therapies (TTs)

MATERIALS AND METHODS

Patients and methods

Between March 5, 2020 and May 18, 2020, all consecutive asymptomatic/pauci-symptomatic patients with cancer scheduled to begin or continue an anticancer treatment at the outpatient facility of the Oncology Division of Papa Giovanni XXIII hospital in Bergamo, Italy, were screened for SARS-CoV-2 infection. All patients signed a dedicated informed consent form, approved by the local ethical committee, and completed a survey questionnaire about signs or symptoms of SARS-CoV-2 infection or overt COVID-19 disease in the previous 2 months.

A two-step diagnostic test for SARS-CoV-2 infection was performed. The rapid lateral flow chromatographic serologic immunoassay for the qualitative detection of

anti-SARS-CoV-2 IgG and IgM was used for all patients. Nasopharyngeal swab RNA reverse transcriptase (RT) PCR assay was then used to search for active infection in cases with IgM/IgG seropositivity. To evaluate the presence of IgG and IgM against SARS-CoV-2, all enrolled subjects were tested with the NADAL® COVID-19 IgG/IgM Test (Moers, Germany) which is a qualitative membrane-based immunoassay for the detection of IgG and IgM antibodies to SARS-CoV-2 in whole blood, serum or plasma specimen (web page of Moers, Germany). Nasopharyngeal swabs were performed by trained nurse practitioners and staff from the hospital's COVID-19 Assessment Team. Presence of SARS-CoV-2 on nasopharyngeal swab specimens was determined by means of real-time RT-PCR. GeneFinder COVID-19 Plus RealAmp Kit (Elitech, Milan, Italy) or Allplex 2019 n-CoV Assay (Seegene, Seoul, South Korea) were used to detect SARS-CoV-2 by amplification of RdRp gene, E gene and N gene as previously reported.¹¹

SARS-CoV-2 positivity was defined by RT-PCR at the nasopharyngeal swab or serologic test. Patients with overt symptomatic COVID-19 disease did not enter this screening but were referred to a specialized team and are not part of the present study population. Since the NADAL® COVID-19 IgG/IgM Test is not strictly a diagnostic tool, to validate the results, a sensitivity analysis was carried out applying a more stringent definition of SARS-CoV-2 status, considering positive-only patients with a nasal swab positive test.

We included all consecutive asymptomatic/pauci-symptomatic patients with cancer who were on or recently ceased ICIs, TTs or CT. We excluded patients who stopped treatment more than 3 months prior to study entry, which was defined as the date of SARS-CoV-2 testing.

The main objective of the study was to investigate whether an asymptomatic or pauci-asymptomatic SARS-CoV-2 infection could significantly increase the burden of adverse events (AEs) and/or serious adverse events (SAEs) in ICIs patients as compared with CT and TTs patients. AEs were classified according to NCI-CTCAE V.5.0 (common terminology criteria for adverse events: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf), while death, life-threatening toxicities, hospitalization (initial or prolonged), disability or permanent damage were considered as SAEs. All AEs and SAEs that occurred during treatment were prospectively collected and reported in this study irrespective of the causal relationship with treatment or SARS-CoV-2 infection. Furthermore, we collected data to determine the proportion of patients who died due to SARS-CoV-2 infection rather than due to other causes.

An exploratory aim was to evaluate the objective response rate (ORR) and disease control rate (DCR) in SARS-CoV-2-positive and SARS-CoV-2-negative patients. For this purpose, only patients who started ICIs no more than 3 months before SARS-CoV-2 testing were included for the analysis of ORR and DCR. ORR was defined as the proportion of patients with a complete response (CR) or

partial response (PR), while the DCR was defined as the proportion of patients with a CR, PR or stable disease.

A validation set (n=21) of patients treated with ICIs were treated at the Istituto Nazionale dei Tumori in Naples, Italy, (14 patients), and at Christie National Health Service Foundation Trust in Manchester, UK, (7 patients). In Naples, similarly to the training cohort, consecutive SARS-CoV2-positive patients treated with ICIs have been collected and SAEs were registered in medical charts; SARS-CoV2 infection was confirmed by nasopharyngeal swab. In Manchester, patients receiving systemic therapy for cancer that presented with potential mild, pauci-symptomatic COVID-19-related symptoms (such as fever and cough) were tested and SARS-CoV2 infection was confirmed by nasopharyngeal swab. Similarly to the training cohort, patients with severe COVID-19 disease were referred to a specialized team and were not included in the present study.

Statistical analysis

The association between SARS-CoV-2 and SAEs/AEs was evaluated by means of χ^2 test or Fisher's exact test, as appropriate.

A χ^2 test for trend (exact p value) to compare the maximum grade for each AE between SARS-CoV-2-positive and SARS-CoV-2-negative patients was performed.

To evaluate if ICIs acted as a confounder on the association between SARS-CoV-2 and AEs/SAEs, a CMH test was performed taking into account the treatment received (ICIs vs CT vs TTs) as the stratification factor. Additionally, to assess whether the odds of AEs/SAEs according to SARS-CoV-2 status was different in ICIs versus CT versus TTs, the Breslow-Day test was performed.

In patients with cancer receiving ICIs, bivariate logistic regression models to estimate the adjusted ORs of SAEs for meaningful covariates, adjusting for the effect of SARS-CoV-2 test result, were performed. In details, we tested known prognostic covariates, such as age, sex, comorbidities, platelet count, lymphocyte count, neutrophils count and neutrophils/lymphocyte (NL) ratio, determined at the time of serologic testing. Moreover, within the subset of SARS-CoV-2-positive subjects, univariate logistic regression models were performed. For continuous variables, the assessment of the linearity of the effect on the logit of the outcome variable was performed by means of the evaluation of the statistical significance of the Wald test of restricted cubic splines added to the model.¹²

Median follow-up time was defined as the time from the start of cancer therapy to the date of death or last available visit.

Statistical analyses were performed using SAS V.9.4. All statistical tests were two-sided and considered significant at p<0.05.

RESULTS

Two hundred and ninety-three consecutive patients were included in this study: 159 received ICIs, 50 received CT and 84 received TTs. Demographic and general

characteristics of patients treated with ICIs, CT or TTs are reported in table 1. The most frequent tumor type in ICIs patients was melanoma (57.2%), followed by non-small cell lung cancer (33.3%), renal cell carcinoma (7.5%) and other malignancies (1.9%). Statistically significant differences between ICIs, CT or TTs were observed for some demographic characteristics, specifically a lower median age in the TTs group compared with ICIs (Wilcoxon p value =0.007) and a higher proportion of men in ICIs and CT compared with TTs (Fisher's p=0.006 for ICIs vs TTs and Fisher's p=0.033 for CT vs TTs) were found. However, apart from the lack of patients with melanoma in the CT group (Fisher's p<0.001), there were no statistically significant differences between ICIs-treated, CT-treated or TTs-treated patients in terms of stage distribution and comorbidities. The median time from the last dose of anticancer treatment to the date of SARS-CoV-2 testing was 23.5 days (first quartile (Q1): 14.0, third quartile (Q3): 42.0) and 21 days (Q1:7, Q3:33) for ICIs and CT, respectively, while it was only 1 hour (Q1:1, Q3: 1) for TTs, due to the oral daily schedule.

The majority of the 159 (78.6%) ICIs patients were treated for advanced disease while the remaining patients were being treated in the adjuvant setting. The ICI was single-agent anti-PD1/programmed death ligand 1 (PDL-1) in 137 (86.2%) patients, combined immunotherapy (anti-cytotoxic T lymphocyte associated protein 4 (CTLA4) plus anti-PD1) in 20 (12.6%) and anti-CTLA4 in 2 patients. Median time from starting ICIs, was 7.1 months (Q1: 3.2, Q3: 14.9). Summary information on tumor therapy history and on hematologic variables is reported in online supplemental tables 1 and 2, respectively. The majority of the CT-treated (80.4%) and TT-treated (82.1%) patients had advanced disease. The median follow-up was 3.9 months (Q1: 2.8, Q3: 7.3) and 12.4 months (Q1: 3.8, Q3: 19.7) in CT and TTs, respectively.

The incidence of SARS-CoV-2 positivity was similar across the three treatment groups: 13 (26.0%) in CT, 24 (28.6%) in TTs and 52 (32.7%) in ICIs, (χ^2 test p=0.610, online supplemental table 3). Among SARS-CoV-2-positive patients, 3 (23.1%) and 10 (41.7%) of CT-treated and TTs-treated patients presented with one or more mild symptoms at the time of testing, most frequently fever. Half of the SARS-CoV-2-positive ICI patients (25 patients, 48.1%) presented with one or more mild symptoms at the time of testing. The most frequent symptom was fever.

Among ICIs-treated patients, 50 (31.5%) experienced an AE. There was no statistically significant association between AE occurrence and SARS-CoV-2 positivity (χ^2 test p=0.222). The most frequent AE was gastrointestinal toxicity (any grade: 15.0% and 7.7% in SARS-CoV-2-negative and SARS-CoV-2-positive patients, respectively). The majority of AEs was low grade; two grade 3 (G3) AEs were reported in SARS-CoV-2-negative patients (one lipase increase, one colitis). In SARS-CoV-2-positive patients two G3 AEs (one asthenia, one staphylococcus infection) and one G4 AE (hepatic toxicity, transaminitis)

Table 1 Patient characteristics

	CT			TT			ICI		
	SARS-CoV-2 negative n=37	SARS-CoV-2 positive n=13	Overall n=50	SARS-CoV-2 negative n=60	SARS-CoV-2 positive n=24	Overall n=84	SARS-CoV-2 negative n=107	SARS-CoV-2 positive n=52	Overall n=159
Age									
Mean (SD)	66.3 (11.7)	63.2 (14.2)	65.5 (12.4)	62.3 (13.7)	61.6 (12.8)	62.1 (13.4)	66.3 (12.5)	66.9 (11.3)	66.5 (12.1)
Median (Q1–Q3)	69.0 (61.0–75.0)	65.0 (58.0–73.0)	67.5 (58.0–75.0)	65.0 (54.5–72.5)	63.5 (53.5–70.0)	63.5 (54.5–71.5)	69.0 (59.0–75.0)	68.0 (62.0–73.5)	69.0 (60.0–75.0)
Min–Max	26.0–84.0	26.0–81.0	26.0–84.0	28.0–88.0	31.0–84.0	28.0–88.0	20.0–89.0	39.0–86.0	20.0–89.0
Sex									
Female	12 (32.4)	4 (30.8)	16 (32.0)	33 (55.0)	10 (41.7)	43 (51.2)	36 (33.6)	16 (30.8)	52 (32.7)
Male	25 (67.6)	9 (69.2)	34 (68.0)	27 (45.0)	14 (58.3)	41 (48.8)	71 (66.4)	36 (69.2)	107 (67.3)
Number of subjects with at least one comorbidity other than cancer	25 (67.6)	8 (61.5)	33 (66.0)	32 (53.3)	11 (45.8)	43 (51.2)	60 (56.1)	28 (53.8)	88 (55.3)
Description of comorbidities:									
Number of comorbidities (n%)									
One comorbidity	17 (68.0)	6 (75.0)	23 (69.7)	24 (75.0)	7 (63.6)	31 (72.1)	39 (65.0)	21 (75.0)	60 (68.2)
More than one comorbidity	8 (32.0)	2 (25.0)	10 (30.3)	8 (25.0)	4 (36.4)	12 (27.9)	21 (35.0)	7 (25.0)	28 (31.8)
Number of patients with cardiac disease	17 (68.0)	5 (62.5)	22 (66.7)	24 (75.0)	8 (72.7)	32 (74.4)	45 (75.0)	26 (92.9)	71 (80.7)
Number of patients with pulmonary disease	6 (24.0)	4 (50.0)	10 (30.3)	8 (25.0)	4 (36.4)	12 (27.9)	22 (36.7)	2 (7.1)	24 (27.3)
Number of patients with chronic kidney disease	2 (8.0)	1 (12.5)	3 (9.1)	5 (15.6)	0 (0.0)	5 (11.6)	5 (8.3)	2 (7.1)	7 (8.0)
Number of patients with diabetes	7 (28.0)	1 (12.5)	8 (24.2)	2 (6.3)	3 (27.3)	5 (11.6)	16 (26.7)	6 (21.4)	22 (25.0)
Number of patients with underlying immunodeficiency	2 (8.0)	0 (0.0)	2 (6.1)	2 (6.3)	0 (0.0)	2 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Cancer details									
Cancer type									
Melanoma	0 (0.0)	0 (0.0)	0 (0.0)	34 (56.7)	18 (75.0)	52 (61.9)	54 (50.5)	37 (71.2)	91 (57.2)
NSCLC	20 (54.1)	9 (69.2)	29 (58.0)	15 (25.0)	3 (12.5)	18 (21.4)	43 (40.2)	10 (19.2)	53 (33.3)

Continued

Table 1 Continued

	CT			TT			ICI		
	SARS-CoV-2 negative n=37	SARS-CoV-2 positive n=13	Overall n=50	SARS-CoV-2 negative n=60	SARS-CoV-2 positive n=24	Overall n=84	SARS-CoV-2 negative n=107	SARS-CoV-2 positive n=52	Overall n=159
RCC	1 (2.7)	2 (15.4)	3 (6.0)	9 (15.0)	3 (12.5)	12 (14.3)	7 (6.5)	5 (9.6)	12 (7.5)
Other	16 (43.2)	2 (15.4)	18 (36.0)	2 (3.3)	0 (0.0)	2 (2.4)	3 (2.8)	0 (0.0)	3 (1.9)
Cancer stage (AJCC v8)									
III	6 (16.2)	4 (30.8)	10 (20.0)	11 (18.3)	4 (16.7)	15 (17.9)	25 (23.4)	15 (28.8)	40 (25.2)
IV	31 (83.8)	9 (69.2)	40 (80.0)	49 (81.7)	20 (83.3)	69 (82.1)	82 (76.6)	37 (71.2)	119 (74.8)

AJCC, American joint committee on cancer ; CT, chemotherapy; ICI, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; Q1, first quartile; Q3, third quartile; RCC, renal cell carcinoma; TT, targeted therapy.

occurred. A higher occurrence of cardiovascular AEs was observed in SARS-CoV-2-positive patients (one patient with G1 elevation of the troponin and two patients with G2 hypertension, online supplemental table 4) compared with SARS-CoV-2-negative patients where no cardiovascular AE was observed.

The proportion of patients who experienced AEs in SARS-CoV-2-positive compared with SARS-CoV-2-negative patients was similar in ICIs (25.00% vs 34.58%), CT (38.46% vs 43.24%) and in TTs (20.83% vs 31.67%) (Breslow-Day test $p=0.9112$). No statistically significant association between occurrence of AEs and SARS-CoV-2 positivity was found in the whole population or by treatment group (CMH test $p=0.123$; Fisher's test $p=1.000$, 0.426, and 0.276 for CT, TTs and ICIs, respectively).

No statistically significant association between rate of AEs and disease stage was found in the overall population (Fisher's exact test $p=0.653$); moreover the incidence of AEs in SARS-CoV-2-positive and SARS-CoV-2-negative patients was similar between stage III (17.4% vs 35.7%) and stage IV (28.8% vs 35.2%) (Breslow-Day test $p=0.340$).

SAEs according to type of treatment

SAEs occurred in 16 (5.5%) patients of the whole population, 11 (12.4%) in the SARS-CoV-2-positive group and 5 (2.5%) in the SARS-CoV-2-negative group. Ten (90.9%) SAEs in the SARS-CoV-2-positive group occurred in patients with advanced disease. SAEs were more frequent in SARS-CoV-2-positive patients when compared with SARS-CoV-2-negative cases (CMH test $p=0.0008$).

The incidence of SAEs in SARS-CoV-2-positive compared with SARS-CoV-2-negative patients was similar in ICIs-treated patients (17.3% vs 3.7%) and the CT group (15.4% vs 2.7%) (Breslow-Day test $p=0.891$) (table 2). In SARS-CoV-2-positive patients, the incidence of SAEs in patients receiving ICIs versus CT was not statistically different (17.3% vs 15.4%, respectively, Fisher's exact test $p=1.000$). No SAEs were observed in SARS-CoV-2-positive or SARS-CoV-2-negative patients receiving TTs.

The most common reason for hospitalization in SARS-CoV-2-positive ICIs-treated patients was pneumonitis in seven out of nine patients, and five of these required oxygen because of shortness of breath and desaturation. In two of these cases, COVID-19 was confirmed by bronchoalveolar lavage. A CT scan showed bilateral multiple peripheral lesions with ground-glass opacity with reticular pattern, consolidation, and fibrotic and subpleural lines (online supplemental figure 1). In all cases, fever was present; in one case renal replacement therapy was needed. Antibiotics and antivirals were administered in six and three patients, respectively. Two patients required glucocorticoids because of dyspnea not responding to oxygen therapy, while in two refractory patients interleukin (IL) 6 blocking therapy was administered (table 3). Among 50 patients treated with CT, 3 (6.0%) patients experienced an SAE, 2 of these were SARS-CoV-2 positive (table 3). One patient was hospitalized, two patients were

Table 2 Comparison of frequency of SAEs according to SARS-CoV-2 test results between treatment received

	CT n=50	TT n=84	ICI n=159	Overall n=293
SARS-CoV-2-positive patients	13 (26.0)	24 (28.6)	52 (32.7)	89 (30.4)
No occurrence of SAE	11 (84.6)	24 (100.0)	43 (82.7)	
Occurrence of SAE	2 (15.4)	–	9 (17.3)	
SARS-CoV-2-negative patients	37 (74.0)	60 (71.4)	107 (67.3)	204 (69.6)
No occurrence of SAE	36 (97.3)	60 (100.0)	103 (96.3)	
Occurrence of SAE	1 (2.7)	–	4 (3.7)	
CMH test*				0.0008*
Breslow-Day test*				0.8909

*Breslow-Day test: tests the homogeneity of the OR between the two groups.

†CMH: Cochran-Mantel-Haenszel test: tests the conditional independence between SAE and SARS-CoV-2 test result controlling for the type of therapy.

.CT, chemotherapy; ICI, immune checkpoint inhibitors; SAE, serious adverse event; TT, targeted therapy.

treated at home with O₂ therapy, and all three patients died of pulmonary complications (table 3).

In patients receiving ICIs, after adjusting for the effect of SARS-CoV-2 positivity, NL ratio and lymphopenia were significantly associated with the occurrence of SAEs (adjusted OR: 1.68, 95% CI 1.19 to 2.36, $p=0.003$ for NL ratio and adjusted OR: 0.11, 95% CI 0.02 to 0.70, $p=0.020$ for lymphocyte count, table 4). In the subgroup of SARS-CoV-2-positive patients, NL ratio showed a statistically significant association with SAEs (OR: 2.76, 95% CI 1.16 to 6.54, $p=0.021$, (online supplemental table 5). In line with the results reported in the whole cohort of ICIs-treated patients, lymphocyte count showed a trend towards statistical significance (OR: 0.90, 95% CI 0.01 to 1.06, $p=0.056$).

The low number of patients and SAEs in the CT and TTs groups precluded any analysis of NL ratio and lymphocyte count as prognostic factors.

Deaths

Eleven patients died, of which eight were SARS-CoV-2 positive. Mortality of SARS-CoV-2-positive patients was statistically significantly higher compared with SARS-CoV-2-negative patients (8/89 vs 3/204, respectively, Fisher's exact test $p=0.004$). The median age of the deceased patients was 72 years (Q1: 58.0, Q3: 80.0), six (54.5%) were women, and six (54.5%) had at least one comorbidity.

In the SARS-CoV-2-positive patients the mortality rate was 11.5% (6/52) and 15.4% (2/13) in the ICIs-patients and CT-patients, respectively (Fisher's test, $p=0.655$). In the ICIs and CT groups all deaths were due to COVID-19 and all patients had advanced disease.

In the ICIs-patients the main cause of death was the acute respiratory distress due to bilateral pneumonitis in all patients. All patients but one were hospitalized, received O₂ therapy and none responded to steroid treatment. Only one patient received supportive care at home, but ultimately died due to respiratory complications. In

all cases, the clinical diagnosis was COVID-19 disease with acute respiratory failure. CT-related deaths were due to due to bilateral pneumonitis.

In the overall population, the incidence of deaths was not statistically significantly different between stages III and IV (1/65 vs 10/228, Fisher's exact test $p=0.466$); however, in stage IV, the incidence of deaths of SARS-CoV-2-positive patients was statistically significantly higher compared with negative cases (12.1% vs 1.2%, Fisher's exact test $p=0.001$).

Incidence of SAEs in the validation cohort

To confirm these results, an external cohort of 21 SARS-CoV-2-positive patients with melanoma treated with ICIs was reviewed. Twelve patients (57.1%) had advanced disease (AJCC stage IV) while the remaining patients were treated in the adjuvant setting. The mean age was 59.6 years, 57.1% were male, 61.9% were ECOG 0 at the time of SARS-CoV-2 serology test and 28.6% had comorbidities. The ICI was single agent anti-PD-1 in 17 (81%) patients and a combined immunotherapy (anti-CTLA-4 plus anti-PD-1) in the remaining 4 patients (19%). Three patients (14.3%) presented with one or more mild symptoms at the time of testing, all of them had fever and cough, or fever and dyspnea/myalgia. Four patients (19.0%) experienced an SAE and were hospitalized, two had pneumonitis, none died. The frequency of SAEs was similar in the study and validation cohorts (17% and 19%, respectively, Fisher's exact test $p=1.000$).

Overall response of patients treated with ICIs during SARS-CoV-2 infection

Among 159 ICI-patients included, 51 (32.1%) started treatment no more than 3 months before the SARS-CoV-2 testing, and for 34 (66.7%, of which 14 were SARS-CoV-2 positive and 20 SARS-CoV-2 negative) patients the tumor assessment after 3 months from testing was available.

The ORR was 21.4% (3 patients with CR/PR, 11 patients with stable disease/PD) in SARS-CoV-2-positive

Table 3 Description of serious adverse events (SAEs)

	CT		TT		ICI		Overall n=293
	SARS-CoV-2 negative n=37	SARS-CoV-2 positive n=13	SARS-CoV-2 negative n=60	SARS-CoV-2 positive n=24	SARS-CoV-2 negative n=107	SARS-CoV-2 positive n=52	
Hospitalizations:							
Yes	0	1 (7.7)	–	–	2 (1.9)	7 (13.5)	10 (3.4)
Number of deaths	–	1 (100.0)			0 (0.0)	4 (57.1)	5 (50.0)
Reasons for hospitalization:							
Patients with radiographic changes, n (%)	–	0 (0.0)			0 (0.0)	7 (100.0)	7 (70.0)
Patients requiring oxygen, n (%)	–	1 (100.0)			0 (0.0)	5 (71.4)	6 (60.0)
Patients requiring renal replacement therapy, n (%)	–	0 (0.0)			0 (0.0)	1 (14.3)	1 (10.0)
Patients requiring antibiotics therapy, n (%)	–	1 (100.0)			0 (0.0)	6 (85.7)	7 (70.0)
Patients requiring antivirals therapy, n (%)	–	0 (0.0)			0 (0.0)	3 (50.0)	3 (33.3)
Missing	–	0			0	1	1
Patients requiring glucocorticoids therapy, n (%)	–	0 (0.0)			0 (0.0)	2 (33.3)	2 (22.2)
Missing	–	0			0	1	1
Patients requiring anti-IL6 therapy, n (%)	–	0 (0.0)			0 (0.0)	2 (33.3)	2 (22.2)
Missing	–	0			0	1	1
Number of deaths, n (%)	1 (2.6)	2 (15.4)	–	–	2 (1.9)	6 (11.5)	11 (3.8)

SARS-CoV-2 positive: one positive result from serologic test confirmed by nasal swab.
CT, chemotherapy; ICI, immune checkpoint inhibitors; TT, targeted therapy.

Table 4 Bivariate logistic regression models—effect of covariates on SAE controlling for SARS-CoV-2 test result—ICI cohort

	N	P value of variable	Adjusted OR (95% CI)
Age	159	0.130	1.05 (0.99 to 1.12)
Sex (female vs male)	159	0.235	2.05 (0.63 to 6.73)
Comorbidity (yes vs no)	159	0.587	1.39 (0.42 to 4.61)
Platelet count	133	0.175	1.01 (1.00 to 1.01)
Lymphocyte count	130	0.020*	0.11 (0.02 to 0.70)
NL ratio	130	0.003*	1.68 (1.19 to 2.36)

Adjusted OR: OR adjusted for the effect of SARS-CoV-2 test result.

ICIs, immune checkpoint inhibitors; NL, neutrophils/lymphocyte; SAE, serious adverse events.

patients and 30.0% (6 patients with CR/PR, 14 patients with stable disease/PD) in SARS-CoV-2-negative patients (Fisher's test, $p=0.704$). The DCR was 78.6% (11 patients with CR/PR/stable disease, 3 patients with PD) in SARS-CoV-2-positive patients and 85.0% (17 patients with CR/PR/stable disease, 3 patients with PD) in SARS-CoV-2-negative patients (Fisher's test, $p=0.672$).

Sensitivity analyses according to nasal swab SARS-CoV-2 status

Considering the more stringent definition of SARS-CoV-2 positivity, based on the results of nasal swab only, the number of SARS-CoV-2-positive patients in the CT and TTs groups decreased from 13 to 3 and from 24 to 8 patients, respectively (online supplemental table 6). On the other hand, serologic positivity was not confirmed for only four patients in the ICIs group. Consequently, the incidence of SARS-CoV-2 positivity was similar for CT and TTs (6.0% and 9.5% respectively, Fisher's exact test $p=0.537$) while it was statistically significantly higher in ICIs (30.2%, Fisher's exact test $p<0.001$ for both comparisons).

In terms of incidence of AEs, SAEs and mortality between SARS-CoV-2-positive and SARS-CoV-2-negative patients, the sensitivity analysis results confirmed our main findings in the whole population, and specifically: (1) No statistically significant association between rate of AEs and SARS-CoV-2 positivity was found (Fisher's exact test $p=0.063$, online supplemental table 7); (2) SAEs were more frequent in SARS-CoV-2-positive patients compared with SARS-CoV-2-negative cases (Fisher's exact test $p=0.001$, online supplemental table 7); (3) Mortality of SARS-CoV-2-positive patients was statistically significantly higher compared with SARS-CoV-2-negative patients (Fisher's exact test $p=0.011$, online supplemental table 7); (4) In patients receiving ICIs, after adjusting for the effect of SARS-CoV-2 positivity, NL ratio and lymphopenia were significantly associated with the occurrence of SAEs (adjusted OR: 1.67, 95% CI 1.19 to 2.35, $p=0.003$ for NL

ratio and adjusted OR: 0.11, 95% CI 0.02 to 0.70, $p=0.019$ for lymphocyte count).

In the subgroup of SARS-CoV-2-positive patients treated with ICIs, the NL ratio showed a statistically significant association with SAEs (OR: 2.67, 95% CI 1.15 to 6.22, $p=0.023$).

DISCUSSION

The three most striking results of the present study are: (1) The SAEs are more frequent in SARS-CoV-2-positive patients compared with SARS-CoV-2-negative cases (CMH test $p=0.0008$); (2) The mortality rate is higher in SARS-CoV-2-positive patients treated with CT or ICIs (11.5% vs 1.9% for ICI-treated patients and 15.4% vs 2.7% in CT, CMH test $p=0.0021$), but not in patients treated with TTs. SARS-CoV-2-positive patients receiving TTs did not experience any SAE; (3) In asymptomatic or pauci-symptomatic SARS-CoV-2-positive patients with cancer receiving ICIs, the incidence of AEs was not increased compared with SARS-CoV-2-negative patients.

Patients with cancer appear to be at increased risk of mortality and severe illness during SARS-CoV-2 infection compared with those without cancer. Kuderer *et al* reported a death rate of 13%, and mortality was higher (40%) in patients with active advanced disease progressing on treatment.⁷ An analysis of 334 patients with cancer from the Mount Sinai Health System reported an 11% rate of death.¹³ A third series of 218 patients with cancer reported a case fatality rate of 28%, although the authors acknowledged a bias towards more severe cases.¹⁴ Our data extend the above results showing that mortality of SARS-CoV-2-positive patients is statistically significantly higher compared with SARS-CoV-2-negative patients (9.0% vs 1.5%, respectively, Fisher's exact test $p=0.004$). In our cohort all deaths in the ICIs and CT groups were due pneumonitis and acute respiratory failure, both strictly related to COVID-19 disease. Considering the increased risk of SAEs in general (hospitalization and deaths) and specifically mortality rate as well, our data suggest the need for increased surveillance and testing for SARS-CoV-2 in all patients with cancer having systemic therapy, because of the increase of severe toxicities.

One of the open issues is the impact of systemic therapies and specifically the burden of SAEs during CT and ICIs. In the study reported by Kuderer *et al*⁷ only 4% of patients had received immunotherapy. Furthermore this was primarily a retrospective cohort study designed for rapid patient accrual and data collection during the COVID-19 pandemic, lacking precise timing for diagnostic and therapeutic procedures, and without data on toxicities. Similarly in the New York study,¹³ no data on cancer treatment and safety were shown.

Our study shows that in patients treated with CT, TTs or ICIs there is no increase in AEs in SARS-CoV-2-positive patients compared with non-infected patients. Interestingly, in patients with cancer receiving CT or ICIs we observed an increase in SAEs but not AEs. There was no

apparent increased risk of immune toxicity (colitis, hepatitis, thyroiditis, etc) seen in SARS-CoV2-positive patients. However, there was an increase in SAEs and these were due to pneumonitis. This might suggest a potential detrimental synergistic effect on the pulmonary toxicity between SARS-CoV-2 infection and CT or ICIs that, in turn, leads to severe pulmonary toxicity.

The natural history of SARS-CoV-2 infection covers three main phases:¹⁵ an initial phase, which is characterized by viral replication and relatively mild symptoms (early infection phase); a second phase with mild respiratory symptoms (pulmonary phase); a third phase with a hyperinflammatory condition.

Based on our results, it is plausible that CT with the intrinsic immunosuppressive mechanism of action may have a negative impact during the viral replication, and ICIs can worsen the inflammatory phase. TTs may have no impact on either the first replicative phase or the second inflammatory phase. Overall, our results support a better tolerability of TTs in SARS-CoV-2-positive patients in terms of SAEs. This could help physicians to better select treatments in patients with cancer with a targetable oncogenic addicted disease.

Our results provide practical suggestions for management of patients with cancer receiving ICIs. Considering that the incidence of SAEs in patients on ICIs is not negligible, clinicians may consider delaying the initiation of therapy in patients with cancer with advanced disease if this is clinically acceptable. In addition temporary discontinuation could be considered in patients with major radiologic response. This may be particularly important in older patients, who, if SARS-CoV-2 positive, are intrinsically at higher risk, as previously reported.⁷

Interestingly and consistently with earlier results showing a correlation between lymphopenia and COVID-19-associated disease severity,¹⁶ in our study patients with lymphopenia and high NL ratio, who were receiving ICIs had a higher risk of developing SAEs. Further studies are needed to confirm if these parameters may be considered predictive biomarkers of toxicity.

The lower incidence of SAEs seen in the adjuvant setting compared with the metastatic setting may reflect the degree of cancer-induced immunosuppression seen in metastatic disease

The main reason for hospitalization was pneumonia. In the context of SARS-CoV-2 positive patients receiving ICIs, one of the main challenges is the differential diagnosis between ICIs-related versus COVID-19-related pneumonitis. Bilateral pneumonia, usually characterized by multiple peripheral lesions with ground-glass opacity with reticular pattern, consolidation, microvascular dilatation and vacuolar images, fibrotic and subpleural lines have been reported in patients with COVID-19 and ICIs. Similarly, COVID-19 and ICIs adverse events share systemic symptoms including fever, cough, fatigue, dyspnea and gastrointestinal symptoms.

The strengths of this study include the relatively large cohorts of patients included, the inclusion of

SARS-CoV-2-positive and SARS-CoV-2-negative patients across major tumor types and systemic therapies, and the use of a validation cohort to confirm the incidence of SAEs in SARS-CoV-2-positive patients receiving ICIs. We are aware of potential limitations since our study is underpowered to identify any potential difference of SAEs in different tumor histologic subtypes and small statistically differences in patients receiving ICIs or other treatments. Furthermore, patients were not stratified according to potential confounders that could impact on treatment-related toxicity. Finally, and most importantly, patients with complicated COVID-19 were not included in our study. Hence we cannot exclude that the overall mortality rate in patients with cancer is higher than that reported in the cohort of patients included in our study.

In conclusion, our study suggests that in asymptomatic or pauci-symptomatic patients, SAEs and mortality rates are higher in SARS-CoV-2-positive cases, and for this reason clinicians should carefully monitor these patients during treatment. TTs are not associated with SAEs and this may be an option in some patients.

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REFERENCES

- Chen N, Zhou M, Dong X, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
- Wang C, Horby PW, Hayden FG, *et al.* A novel coronavirus outbreak of global health concern. *Lancet* 2020.
- Hamming I, Timens W, Bultuis MLC, *et al.* Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;203:631–7.
- Zhou P, Yang X-L, Wang X-G, *et al.* Addendum: a pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;588:E6.
- Kamboj M, Sepkowitz KA. Nosocomial infections in patients with cancer. *Lancet Oncol* 2009;10:589–97.
- 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.
- Kuderer NM, Choueiri TK, Shah DP, *et al.* Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet* 2020;395:1907–18.
- Vabret N, Britton GJ, Gruber C, *et al.* Immunology of COVID-19: current state of the science. *Immunity* 2020;52:910–41. Volume.
- Zheng H-Y, Zhang M, Yang C-X, *et al.* Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cell Mol Immunol* 2020;17:541–3.
- Zheng M, Gao Y, Wang G, *et al.* Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol* 2020;17:533–5.
- Corman VM, Landt O, Kaiser M, *et al.* Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill* 2020;25:2000045.
- . Available: https://www.lexjansen.com/sesug/2019/SESUG2019_Paper-233_Final_PDF.pdf
- Miyashita H, Mikami T, Chopra N, *et al.* Do patients with cancer have a poorer prognosis of COVID-19? an experience in New York City. *Ann Oncol* 2020;31:1088–9.
- Mehta V, Goel S, Kabarriti R, *et al.* Case fatality rate of cancer patients with COVID-19 in a new York hospital system. *Cancer Discov* 2020;10:935–41.
- Romagnoli S, Peris A, De Gaudio R, and Geppetti P SARS-COV-2 and COVID-19: from the bench to the bedside. *Physiol Rev* 2020;100:1455–66.
- Wang F, Nie J, Wang H, *et al.* Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *J Infect Dis* 2020;221:1762–9.

Correction: SARS-CoV-2 infection and adverse events in patients with cancer receiving immune checkpoint inhibitors: an observational prospective study

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