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COVID-19 risk for patients undergoing anticancer treatment at the outpatient clinic of the National Cancer Institute of Milan: the COVINT study

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ABSTRACT

Background In the midst of the COVID-19 pandemic, patients with cancer are regarded as a highly vulnerable population. Overall, those requiring hospital admission for treatment administration are potentially exposed to a higher risk of infection and worse outcome given the multiple in-hospital exposures and the treatment immunosuppressive effects.

Methods COVINT is an observational study assessing COVID-19 incidence among patients receiving anticancer treatment in the outpatient clinic of the Istituto Nazionale dei Tumori di Milano. All consecutive patients with non-haematological malignancies treated with intravenous or subcutaneous/intramuscular anticancer therapy in the outpatient clinic were enrolled. The primary endpoint is the rate of occurrence of COVID-19. Secondary endpoints included the rate of COVID-19-related deaths and treatment interruptions. The association between clinical and biological characteristics and COVID-19 occurrence is also evaluated. COVID-19 diagnosis is defined as (1) certain if confirmed by reverse transcriptase PCR assay of nasopharyngeal swabs (NPS); (2) suspected in case of new symptoms or CT scan evidence of interstitial pneumonia with negative/not performed NPS; (3) negative in case of neither symptoms nor radiological evidence.

Results In the first 2 months (16 February–10 April 2020) of observation, 1081 patients were included. Of these, 11 (1%) were confirmed and 73 (6.7%) suspected for COVID-19. No significant differences in terms of cancer and treatment type emerged between the three subgroups. Prophylactic use of myeloid growth factors was adopted in 5.3%, 2.7% and 0% of COVID-19-free, COVID-19-suspected and COVID-19-confirmed patients (p=0.003). Overall, 96 (8.9%) patients delayed treatment as a precaution for the pandemic. Among the 11 confirmed cases, 6 (55%) died of COVID-19 complications, and anticancer treatment was restarted in only one.

Conclusions During the pandemic peak, accurate protective measures successfully resulted in low rates of COVID-19 diagnosis, although with high lethality. Prospective patients' surveillance will continue with NPS and serology testing to provide a more comprehensive epidemiological picture, a biological insight on the impact of cytotoxic treatments on the immune response, and to protect patients and healthcare workers.

Key questions

What is already known about this subject?

- The COVID-19 pandemic is a global health emergency that has forced a reorganisation of most healthcare structures.
- Patients with cancer represent a highly vulnerable population, given the disease, the treatments and the need for multiple in-hospital visits.

What does this study add?

- During the pandemic peak, protective measures put in place both for patients and healthcare staff resulted in a low incidence (1%) of COVID-19 among patients receiving anticancer treatment in the outpatient clinic.
- Among 11 (1%) COVID-19-affected patients, 6 (55%) died due to the infection.
- Of the treated patients, 6.7% were suspected but not confirmed for COVID-19, resulting in significant treatment temporary or definitive discontinuations.

How might this impact on clinical practice?

- Our study provides real-world data about the rate of occurrence of COVID-19 in patients requiring in-hospital administration of anticancer treatments during the COVID-19 pandemic peak. Future studies will evaluate the role of intensive testing for SARS-CoV-2 infection and its impact on cancer patients' outcomes.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in December 2019 as the emergent pathogen in a cluster of patients with pneumonia of unknown cause in the Chinese city of Wuhan, rapidly spread from an epidemic in China to a pandemic, becoming a global emergency.[1] Following China, Italy, and in particular

the Lombardy region, has been one of the largest and most serious clusters of COVID-19 in the world. As of 21 September 2020, 299 506 cases have been reported in Italy, of whom 104 848 in Lombardy.

In this scenario, the pandemic posed several challenges for oncology services.[2] Patients with cancer are known to be more sensitive to infections than healthy people and patients without cancer; this predisposition has historically been related to the immunosuppressive state caused by the malignancy itself and active anticancer treatments such as chemotherapy. Their risk is also increased by the need of multiple in-hospital visits, considering that at least 29% of infections in patients with cancer seem to be contracted in hospital.[3] Furthermore, recent evidence shows that not only patients with cancer have a higher risk of developing serious COVID-19-related events than the population without cancer[3–10] but also a higher mortality.[11 12] This risk can be easily lowered in patients receiving oral anticancer treatments, by rescheduling or transitioning outpatient visits to telemedicine and home drug delivery.[13] Conversely, patients with cancer undergoing intravenous treatments require multiple hospital admissions and are exposed to several contacts with doctors, nurses and healthcare assistants, and with each other. As documented by recent surveys, most hospitals progressively adopted similar protective measures after the pandemic broke out.[13–15]

To date, it is not known if these containment efforts were effective for these patients, in particular at the pandemic peak. At the same time, the discontinuation of oncological treatments driven by the fear of COVID-19 is equally dangerous to patients with cancer.[16] Therefore, to ensure the continuity of cancer care, balancing the risk of in-hospital transmission of COVID-19 and the disruption of proper anticancer strategies is of vital importance. Based on these considerations, the main objective of this observational study is to evaluate the rate of occurrence of COVID-19 in patients undergoing systemic anticancer treatment in the outpatient clinic of the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano (National Cancer Institute of Milan, INT),[17] providing evidence from a comprehensive cancer centre located in the heart of the COVID-19 pandemic.

MATERIALS AND METHODS

We conducted a monocentric, observational study to investigate the incidence of COVID-19 in patients undergoing medical anticancer treatment in the INT outpatient clinic between February and April 2020.

All consecutive patients who received anticancer treatment in the INT outpatient clinic between 16 February and 10 April 2020 were included in this analysis. The main enrolment criteria consisted of the following: (1) age >18 years; (2) histologically proven diagnosis of active solid malignancy; (3) anticancer treatment administered intravenously or subcutaneously/intramuscular in the outpatient clinic setting. Eligible treatments included systemic chemotherapy, immunotherapy and monoclonal antibodies (ie, antivascular agents, anti-Human Epidermal Growth Factor Receptor 2 (HER2)/anti-Epidermal Growth Factor Receptor(EGFR) target therapies), antibody-drug conjugates (ie, trastuzumab emtansine) or endocrine treatments. Patients receiving oral anticancer treatments were considered only if oral therapy is part of a treatment regimen that also includes intravenous or subcutaneous therapy. Patients receiving systemic treatment for haematological cancers (eg, lymphoma, acute leukemias, myeloma) or undergoing oral-only anticancer treatments were excluded from the analysis.

Clinical and biological variables were collected by patients' phone-based follow-up and medical records review.

The primary study endpoint was the incidence of COVID-19 diagnosis, considered as:

- Certain: SARS-CoV-2 infection confirmed by real-time reverse transcriptase-PCR (RT-PCR) assay of nasopharyngeal swabs (NPS) with or without CT scan evidence of pathognomonic of SARS-CoV-2-related interstitial pneumonia (ie, ground-glass opacity and bilateral patchy shadowing).
- Suspected: Patients put in isolation due to new onset of SARS-CoV-2-related symptoms (fever >37.5°C, nasal and/or conjunctival congestion, cough, shortness of breath, diarrhoea, myalgia and/or arthralgia) and/or CT scan evidence of interstitial pneumonia deemed as highly suggestive for COVID-19 but to whom NPS was negative or not performed.

Secondary objectives were (1) to assess the difference in number of patients and visits during the pandemic peak compared with same timeframe in 2019; (2) to investigate the association between patients' and treatment characteristics and COVID-19 occurrence; (3) to evaluate the impact of COVID-19 diagnosis (suspected or certain) on anticancer treatment prosecution and patients' survival. COVID-19 was considered as the cause for anticancer treatment suspension/delay if no other cancer-related or treatment-related toxicity occurred and if the treatment was not completed before its interruption. Death was considered as COVID-19 related if there is no other plausible cause (ie, treatment toxicities, traumas or other acute medical events), cancer was considered as stable and not life-threatening in the immediate future, or if postmortem autopsy was performed ruling out other causes; (4) finally, the incidence of COVID-19 diagnosis in patients hospitalised in the inpatient clinic during the same timeframe is also reported.

Standard descriptive statistics were used to summarise clinical and biological patients' characteristics. Comparisons between patients with confirmed, suspected or negative COVID-19 status were evaluated with the Fisher's exact test and Kruskal-Wallis test, as appropriate. Data cut-off was 17 April 2020. The statistical significance threshold was set to a two-tailed 0.05 value. R software (V.3.6.1) and RStudio software (V.1.2.5033) were used for statistical analyses.

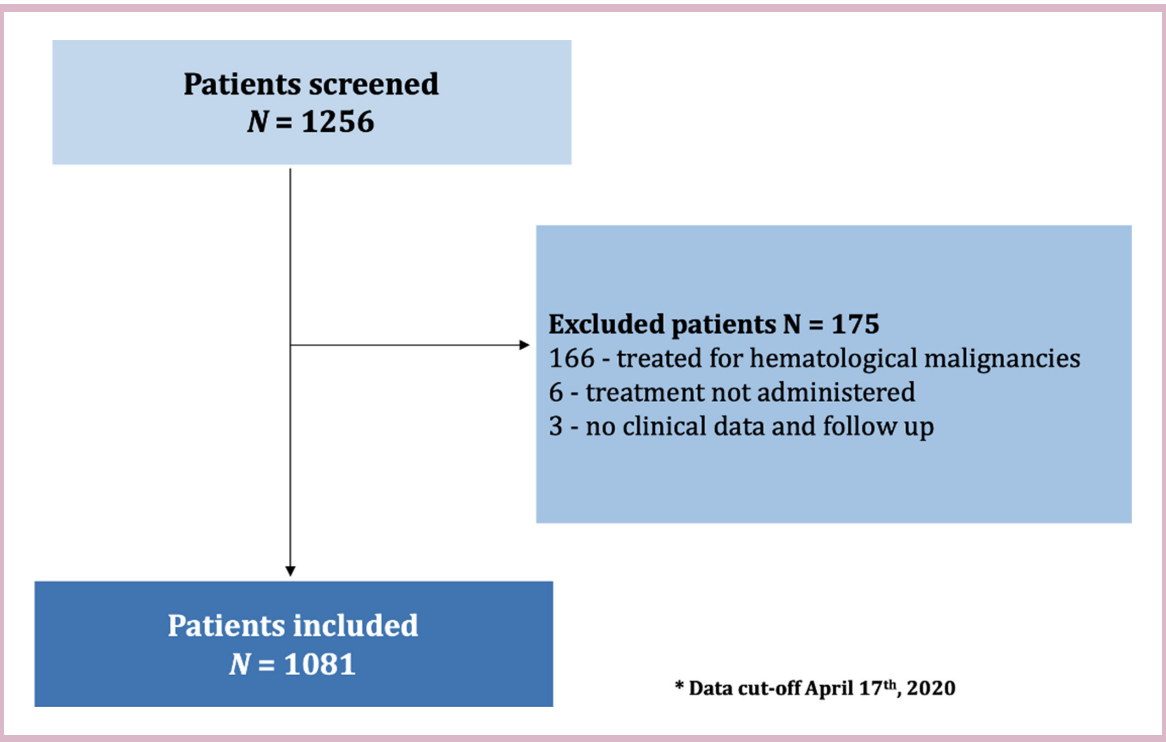

Figure 1 Study flowchart.

The present study was conducted in accordance with the Declaration of Helsinki. Written informed consent was waived in light of the urgent need to collect data.

RESULTS

Study population

The study CONSORT (Consolidated Standards of Reporting Trials) diagram is shown in figure 1. A total of 1256 patients was evaluated for the COVINT study. Of these, 6 patients were excluded due to the lack of at least one treatment administration during study treatment, 3 patients due to lack of clinical and follow-up data, while 166 patients were excluded since treated for haematological malignancies. Finally, 1081 eligible patients treated between 16 February and 10 April 2020 were included in the study, for a total of 2593 treatment administrations and a median of 2 (range 1–11) administrations for each patient. In the same timeframe in 2019, 1266 (+15%) patients were treated in the clinic, for a total of 2865 (vs 2593, +9.5%) administrations and a median of 2 (range 1–9) administrations per patient.

Baseline patient and disease characteristics are displayed in table 1. Overall, 11 (1%) patients had confirmed COVID-19 diagnosis, as they all were symptomatic and tested positive at the NPS test; 73 (6.7%) patients were suspected but not confirmed for COVID-19. CT scan evidence of interstitial pneumonia represented a strong driver to recommend the execution of NPS tests. Indeed, 28 of 33 (85%) patients with positive CT findings underwent the RT-PCR-based test (see online supplemental table 1), compared with only 38 of 87 (42%) of patients with symptoms.

Overall, 96 (8.9%) patients interrupted anticancer treatment (temporarily or permanently, ie, at least one treatment administration was omitted) as the risk of SARS-CoV-2 infection linked to hospital and treatment exposure was deemed higher than the benefit of the therapy.

The most represented disease subtype was breast cancer, followed by thoracic and gastrointestinal tumours. No significant differences according to cancer type and stage, or treatment regimen and line emerged. The association between the number of outpatient clinic visits (ie, treatment administrations) and COVID-19 status was clearly biassed by the fact that patients who did not develop any symptom were able to return and continue with their treatment. Of note, COVID-19-free patients were more frequently treated with growth factors specifically prescribed to reduce the risk of neutropenia during the COVID-19 emergency.

Nineteen patients died during the study period. In detail, 6 patients died of COVID-19, 11 for cancer progression and 2 for other causes.

COVID-19-suspected cases

Among 73 COVID-19-suspected patients, 63 (86.3%) had suggestive symptoms, 46 (63.0%) performed a chest CT scan and 23 (31.5%) had positive findings; 30 (41.1%) underwent NPS, resulting negative. Thirty-three (45.2%) patients were put in quarantine for at least 14 days, and 28 (38.4%) had their anticancer treatment interrupted

Table 1 Patients' characteristics in the whole study cohort and according to COVID-19 status

Characteristics	All N=1081	COVID-19 confirmed N=11	COVID-19 free N=997	COVID-19 suspected N=73	P value
Age (median, range)	63 (19–91)	61 (35–81)	63 (19–91)	63 (28–83)	0.96
Gender					
Female	590 (54.6)	7 (63.6)	543 (54.5)	40 (54.8)	0.89
Male	491 (45.4)	4 (36.4)	454 (45.5)	33 (45.2)	
Tumour type					
Breast	322 (29.8)	4 (36.4)	296 (29.7)	22 (30.1)	0.29
Colorectal	111 (10.3)	–	101 (10.1)	10 (13.7)	
Gastric	49 (4.5)	1 (9.1)	43 (4.3)	5 (6.8)	
Head and neck	59 (5.5)	–	53 (5.3)	6 (8.2)	
Lung	145 (13.4)	1 (9.1)	128 (12.8)	16 (21.9)	
Melanoma	145 (13.4)	2 (18.2)	139 (13.9)	4 (5.5)	
Mesothelioma	18 (1.7)	–	17 (1.7)	1 (1.4)	
NET	17 (1.6)	–	15 (1.5)	2 (2.7)	
Pancreatic	17 (1.6)	–	17 (1.7)	–	
Prostate	14 (1.3)	–	14 (1.4)	–	
Renal	17 (1.6)	–	17 (1.7)	–	
Sarcoma	47 (4.3)	2 (18.2)	45 (4.5)	–	
Urothelial	78 (7.2)	1 (9.1)	73 (7.3)	4 (5.5)	
Others	42 (3.9)	–	39 (3.9)	3 (4.1)	
Disease stage					
II	81 (7.5)	1 (9.1)	76 (7.6)	4 (5.5)	0.95
III	163 (15.1)	1 (9.1)	151 (15.1)	11 (15.1)	
IV	837 (77.4)	9 (81.8)	770 (77.2)	58 (79.5)	
No of visits (median, range)	2 (1–11)	1 (1–4)	2 (1–11)	2 (1–6)	**0.03**
1	282 (26.1)	8 (72.7)	243 (24.4)	31 (42.5)	
2	419 (38.8)	2 (18.2)	389 (39.0)	28 (38.4)	
3	224 (20.7)	–	217 (21.8)	7 (9.6)	
≥4	156 (14.4)	1 (9.1)	148 (14.8)	7 (9.6)	
Chemotherapy					
Overall	447 (41.4)	5 (45.5)	407 (40.8)	35 (47.9)	0.57
Single agent	240 (22.2)	3 (27.3)	222 (22.3)	15 (20.5)	
Doublet	176 (16.3)	2 (18.2)	156 (15.6)	18 (24.7)	
Triplet	31 (2.9)	–	29 (2.9)	2 (2.7)	
Target therapy	261 (24.1)	–	240 (24.1)	21 (28.8)	0.09
Endocrine therapy	114 (10.5)	2 (18.2)	107 (10.7)	5 (6.8)	0.33
Immunotherapy	493 (45.6)	4 (36.4)	453 (45.4)	36 (49.3)	0.67
Line of treatment					
Neoadjuvant	45 (4.2)	–	44 (4.4)	1 (1.4)	0.71
Adjuvant	164 (15.2)	2 (18.2)	150 (15.0)	12 (16.4)	
1st line	450 (41.6)	5 (45.5)	415 (41.6)	31 (42.5)	
2nd line	216 (20.0)	2 (18.2)	203 (20.4)	10 (13.7)	
≥3rd line	206 (19.1)	2 (18.2)	185 (18.6)	19 (26.0)	
Treatment suspension					
Overall	301 (27.8)	11 (100.0)	246 (24.7)	44 (60.3)	**<0.001**

Continued

Table 1 Continued

Characteristics	All N=1081	COVID-19 confirmed N=11	COVID-19 free N=997	COVID-19 suspected N=73	P value
Precautionary	95 (8.8)	–	67 (6.7)	28 (38.4)	
Completed	72 (6.7)	–	66 (6.6)	6 (8.2)	
COVID-19	11 (1.0)	11 (100.0)	–	–	
Transferred	25 (2.3)	–	25 (2.5)	–	
Toxicity	29 (2.7)	–	27 (2.7)	2 (2.7)	
Disease progression	36 (3.3)	–	32 (3.2)	4 (5.5)	
Other reason	33 (3.1)	–	29 (2.9)	4 (5.5)	
Use of growth factors*	55 (5.8)	–	53 (5.3)	2 (2.7)	**<0.001**
Nasopharyngeal swabs					
Not performed	1028 (95.1)	–	984 (98.7)	43 (58.9)	**<0.001**
Negative	43 (4.0)	–	13 (1.3)	30 (41.1)	
Positive	11 (1.0)	11 (100.0)	–	–	
COVID-19-related symptoms	86 (8.0)	11 (100.0)	16 (1.6)	63 (86.3)	**<0.001**
Fever	77 (7.1)	11 (100.0)	21 (2.1)	46 (63.0)	**<0.001**
Rhinitis	16 (1.5)	1 (9.1)	1 (0.1)	14 (19.2)	**<0.001**
Ageusia	6 (0.6)	1 (9.1)	–	5 (6.8)	**<0.001**
Anosmia	9 (0.8)	4 (36.4)	–	6 (8.2)	**<0.001**
Cough	29 (2.7)	4 (36.4)	6 (0.6)	32 (43.8)	**<0.001**
Shortness of breath	42 (3.9)	3 (27.3)	7 (0.7)	20 (27.4)	**<0.001**
Diarrhoea	15 (1.4)	1 (9.1)	9 (0.9)	5 (6.8)	**<0.001**
Myalgia	12 (1.1)	2 (18.2)	3 (0.3)	7 (9.6)	**<0.001**
CT scan					
Not performed	738 (68.3)	1 (9.1)	708 (71.0)	27 (37.0)	**<0.001**
Negative	312 (28.9)	–	289 (29.0)	23 (31.5)	
Positive	31 (2.9)	10 (90.9)	–	23 (31.5)	
Quarantine	37 (3.4)	4 (36.4)	–	33 (45.2)	**<0.001**

Data are presented as n (% of columns), unless otherwise specified.
*Precautionary use due to COVID-19 outbreak.
NET, neuroendocrine tumours.

due to suspected SARS-CoV-2 infection. Of these, only 22 (30.1%) patients restarted their treatment, with a median interval from the last treatment administration before COVID-19 suspect of 50 days. Four of these patients died, all due to cancer progression.

COVID-19-positive cases

Detailed description of COVID-19-positive patients is reported in table 2. Among these, only four were male, with a median age of 62 years. The majority had advanced stage tumours (III-IV), but with no clear prevalence of one tumour or treatment type.

All patients had symptoms of COVID-19, and only one did not undergo hospitalisation and CT scan. In order to maintain the institute as a COVID-free hospital, patients diagnosed with COVID-19 were moved to other hospitals and treated according to best clinical practice. Details about the management of each patient are reported in online supplemental table 2. Of note, only one patient was admitted to the intensive care unit. At the data cut-off, symptoms resolved in three patients, and anticancer treatment was restarted only in one case (55 days after the last chemotherapy administration). Six (55%) patients died of COVID-19, with one death due to ischaemic complications. Of note, the time interval between the last in-hospital visit and first COVID-19 symptoms was shorter (10 (range 4–13) vs 14 (range 7–21) days) in these six patients.

Inpatient clinic report

During our observation timeframe, a total of 130 patients were hospitalised in our inpatient clinic, with a median of 1 (range 1–6) hospitalisation for each patient and a total number of hospitalisations equal to 181. Of these, 41 were also included in our outpatient cohort, including three cases that were later considered as suspected for

Table 2 COVID-19 confirmed patients' characteristics

Patient number	Gender	Age	Type of cancer	Stage	ECOG PS	Smoker	Comorbidities	Concomitant medications	Anticancer treatment	No of outpatient visits	Interval from last treatment administration (days)	Survival status
01	M	62	Urothelial	IV	0	Former smoker	Arterial hypertension, diabetes mellitus type II, hyperuricaemia	Doxasozin, nebivolol, metformin+sitagliptin, rosuvastatin, allopurinol	Durvalumab	1	14	Alive
02	F	61	Breast	IV	0	No	Arterial hypertension, anxious-depressive syndrome	Bisoprolol, prophylactic LMWH, tapentadol	Gemcitabine	1	15	Alive
03	F	35	Sarcoma	IV	0	Former smoker	None	Tapentadol	Ifosfamide	4	7, chemotherapy ongoing in continuous infusion	Alive
04	F	62	Breast	II	0	No	Left nefrectomy with splenectomy for previous renal cancer, autoimmune thyroiditis, hypercolesterolaemia	Cardioaspirin, levothyroxine, statin	Doxorubicin+ cyclophosphamide	1	8	Dead
05	F	82	Breast	IV	1	NA	Arterial hypertention, previous deep vein thrombosis, previous TIA, Raynaud's phenomenon, non-specific arthritis	Cardioaspirin, zofenopril, cholecalciferol	Fulvestrant	1	13	Dead
06	F	50	Melanoma	IV	0	No	Chronic gastritis, left bundle branch block	None	Pembrolizumab	2	21	Alive
07	M	78	Melanoma	III	1	Former smoker	Hypertrophic obstructive cardiomyopathy, arterial hypertension, impaired glucose tolerance, obesity, hyperuricaemia	Bisoprolol, cardioaspirin, ramipril, allopurinol	Nivolumab	1	12	Dead
08	F	54	Gastric	IV	1	NA	None	Pantoprazol, paracetamol+codeine	5FU+oxaliplatin	2	10	Alive
09	F	55	Breast	IV	2	No	Hysterectomy and salpingectomy for endometriosis	Bisoprolol, cholecalciferol	Fulvestrant+palbociclib	1	5	Dead
10	M	64	Sarcoma	IV	1	Former smoker	Arterial hypertension, peripheral arterial occlusive disease	Enalapril+indapamide, cilostazol, atenolol	Ifosfamide	1	12	Dead
11	M	78	Lung	IV	1	Former smoker	Abdominal aortic aneurysm, arterial hypertension, Prinzmetal angina, COPD	Cardioaspirin, atorvastatin, diltiazem, doxazosin, nitroglycerin, glicopyrronium, dutasteride	Pembrolizumab	1	4	Dead

COPD, Chronic obstructive pulmonary disease ; LMWH, Low Molecular Weight Heparin; TIA, Transient Ischemic Attack.

COVID-19. In these three cases, symptoms or radiological signs suspected for COVID-19 appeared more than 14 days after discharge, so that hospitalisation was not considerable as a potential source of contagion. Of all 130 patients, 4 (3.1%) developed symptoms suspected for COVID-19 during hospitalisation, and 1 (0.8%) had ground glass at CT scan. Only 1 (0.8%) patient was diagnosed with COVID-19 1 week after discharge and died of respiratory failure. Detailed characteristics of hospitalised patients are provided in online supplemental table 3.

In the same timeframe in 2019, 166 (+22%) patients were hospitalised, for a total of 226 hospitalisations (+20%).

DISCUSSION

The novel coronavirus pandemic has globally jeopardised the equilibrium of the healthcare systems in several countries. Italy, and in particular the Lombardy region, has been deeply affected, with a large number of severely ill people needing intensive care.[18] In this scenario, the continuity of care for non-communicable diseases such as cancer became more difficult, both for the reduction of available human and structural resources and because hospitals represented a major source of contagion.

In the COVINT study, we aimed to analyse the occurrence rate of COVID-19 in patients undergoing anticancer treatment at the outpatient clinic of our institution from mid-February to mid-April, the time window that witnessed the pandemic peak in Northern Italy. The National Cancer Institute of Milan underwent a profound reorganisation of clinical activities and several protective measures were urgently adopted, as recently reported.[17 19 20] Among these, special measures were taken for patients candidate to receive intravenous or subcutaneous/intramuscular anticancer treatments in the outpatient clinic. In detail, treatment regimens and schedules were modified to prioritise oral or subcutaneous above infusion-based treatments; temporary breaks or reductions in the frequency of administrations were decided on a per-patient basis[14 21]; visits for patients on follow-up or receiving oral treatments were postponed or performed via telephone calls or emails, with the shipment of stocks of drugs directly to the patients' home. Patients were encouraged to perform blood tests outside the hospital and were called the day before each appointment and recommended not to come if they had symptoms suggestive of COVID-19. These cases were included in the COVINT study, and considered as suspected unless both an NPS test and a chest CT scan resulted negative; a triage centre at the entrance of the hospital was installed, to rule out COVID-19 symptoms (again), measure body temperature and provide surgical masks and hand washing. Patients with suspected symptoms for COVID-19 were not admitted to the inpatient or outpatient clinic and were sent back to their homes in quarantine or managed in a dedicated COVID-19 area of the hospital. Once inside the hospital, patients had to follow strict rules for social distancing and caregivers were not admitted to outpatient facilities. Similarly, the inpatient clinic underwent a significant reorganisation, as double and triple rooms have been converted to single rooms, with a consequent reduction in the number of hospitalised patients; moreover, from May onwards, a negative NPS test performed within 48 hours was deemed necessary for all patients requiring hospitalisation. Since February, all healthcare professionals were equipped with surgical masks and gloves. All these measures resulted in the marked reduction in terms of number of admitted patients and treatment administrations compared with the same timeframe in 2019. These measures were consistently adopted worldwide, as demonstrated by recent surveys reporting similar methods to contain COVID-19 spread within oncological centres.[13 15] Overall, clinical practice of medical oncologists was significantly altered, with less dose-dense and dose-intense treatments being preferred to protect patients from the risk of infection.[14]

In our study, we found that only 1% of patients had a confirmed diagnosis of COVID-19, both in the inpatient and outpatient clinic cohorts. To date, data on COVID-19 prevalence in patients with cancer are still heterogeneous. Yu and colleagues[2] recorded a prevalence of COVID-19 <1% (12 out of 1524 patients), among patients with cancer admitted to the Zhongnan hospital from 30 December 2019 to 17 February 2020. Conversely, the prevalence of tumours among patients with COVID-19 varies between 1% and 6% in Asian cases[3] and increases up to 18% in Western series.[4–6] These studies have limits due to the small sample size, the heterogeneity of the objectives, the selection of patients with COVID-19 (eg, only critically ill patients; only hospitalised patients) and the different study periods. Our low rate is reassuring, suggesting that the accurate protective measures adopted were efficient. Nonetheless, this low incidence still had a price: first, the lethality in confirmed cases was high, as >50% of the infected patients died of COVID-19; this is in line with recent analyses, showing a COVID-19-related mortality rate ranging around 25% in patients with cancer, which was also found to be significantly higher compared with non-cancer cases[11 12]; second, 73 (6.7%) patients had a clinical or radiological suspicion of COVID-19 that has not been confirmed; a large portion of these patients were certainly not affected by COVID-19, but the fear of infection caused delays or the permanent discontinuation of anticancer treatments; finally, although inevitable in the short term, the number of treatments administered in these 2 months was significantly less than in the same period of 2019. All these alterations in the daily clinical practice have been performed on a single-patient basis with an accurate selection, with the aim of minimising the risk/benefit ratio. However, even though difficult to assess now, the COVID-19 shock might have a significant medium-long-term impact on the outcome of patients with cancer.

In our report, we found no significant differences according to cancer type and stage, treatment regimen

and line between COVID-positive and COVID-negative population, as in recent reports.[8 10] Given the multiple comorbidities and the anticancer treatments that affected patients were receiving (which included also immunotherapy and endocrine treatments, unlikely to foster COVID-19 worsening), we are convinced that the infection and its outcome were more probably related to the overall frailty of these patients, and were not directly caused by treatment (see table 2). In this light, we do believe that the risk of COVID-19 and its complications is higher in the most fragile patients, especially those with advanced, more aggressive cancers.[9] In addition, only one patient was admitted to ICU, suggesting that a cancer diagnosis represented a criterion to select patients for intensive care.[9] The small number of confirmed COVID-19 cases clearly limit our observation. Indeed, while single centre reports represent a relevant source of documentation for the extraordinary events of these months, joint multicentre analyses will be vital to get to a deeper understanding of the impact of COVID-19 on the cancer patient population. Our study clearly has many limitations. First, with the aim of focusing on the role of the outpatient clinic as a potential source of COVID-19 contagion, we excluded patients who did not receive treatments during our observed period. This choice may have represented a bias, as some patients (especially more frail ones), whose treatment has been postponed, remodelled orally or even not performed at all (ie, adjuvant treatments), could otherwise have contracted COVID-19 in the outpatient clinic with serious consequences. To slightly reduce this bias, we started our observation before the pandemic openly broke out and the consequent lockdown (16 February), thus including a timeframe in which the clinicians neither postponed nor converted the treatments as a COVID-19 containment effort. Second, our results can be biassed due to low number of NPS performed. Above all, over 50% of patients with suspected COVID-19 did not have a swab, so that the reported COVID-19 incidence cannot be accurate. This represents a major limitation not only of our work, but above all of the emergency management in the Lombardy region during the pandemic peak. Indeed, the first results of the national serological test campaign[22] showed that the number of people who came into contact with the virus is six times higher than cases intercepted with NPS tests, with a prevalence of 7.5% of the population in Lombardy against 2.5% nationally. With the aim of providing a clearer epidemiological picture, alive patients enrolled in the COVINT study without a confirmed diagnosis of COVID-19 are being recalled and serologically tested within an amendment of the protocol. The result of this further analysis will be available by the end of 2020 and clearly will not eliminate the problem, as some patients may have had contact with the virus in the months following our observation, but it will give a more complete picture of our cohort.

Our focus is now to the near future. The upcoming phase sees a sustainable trend of COVID-19 diagnoses and deaths in Italy, with a new, slow raise in daily new cases and around only 3% of all performed NPS resulting positive in the general population. In this scenario, we will witness a progressive increase in the number of patients' visits and administered anticancer treatments. So, a continuous COVID-19 screening for patients with cancer is required. At INT, a comprehensive COVID-19 surveillance programme for patients undergoing myelotoxic treatments will be adopted, based on the combination of simple screening measures (phone and in-hospital triage with body temperature check) and testing with RT-PCR test plus serology before any treatment cycle. Indeed, the association of an ELISA-based serological test with NPS could help to generate a more precise epidemiological picture of the contagion and the protective immunity in this population. Furthermore, even if in a first post-peak phase this programme could show a very low prevalence of COVID-19-positive patients, it will serve as the optimal preparation to guarantee the continuity of oncological treatments in the face of a new outbreak scenario.[23] Finally, the longitudinal study of the serology profile of these patients can provide relevant information about the duration of the anti-COVID-19 immune response, and how it is affected by the tumour and the myelotoxic treatments.

CONCLUSIONS

The COVID-19 pandemic significantly altered the continuum of care for patients with cancer. In our institution's outpatient clinic, accurate protective measures assured a low incidence of COVID-19-infected cases, but with a high lethality in affected cases. In the coming months, prospective surveillance with NPS and serology testing will provide a comprehensive epidemiological picture of the infection and will assess if this evidence-based method to protect patients and healthcare operators is cost-effective compared with a simple symptoms screening. Finally, it will generate new information about the impact that each entity, cancer or COVID-19, has on the other.

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