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COVID-19 in Patients with Hematologic Disorders Undergoing Therapy: Perspective of a Large Referral Hematology Center in Rome

Corrado Girmenia[a] Giuseppe Gentile[a] Alessandra Micozzi[a] Luigi Petrucci[a] Francesco Malaspina[a] Alessio Di Prima[a] Erminia Baldacci[a] Simona Bianchi[a] Pellegrina Pugliese[b] Ombretta Turriziani[c] Guido Antonelli[c] Vincenzo Tombolini[d] Robin Foà[a] Maurizio Martelli[a]

[a]Hematology, Department of Hematology, Oncology and Dermatology, AOU Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; [b]Thalassemia Unit, Immunohematology and Transfusion Medicine Unit, AOU Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; [c]Laboratory of Virology, Department of Molecular Medicine, AOU Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; [d]Radiotherapy, Department of Hematology, Oncology and Dermatology, AOU Policlinico Umberto I, Sapienza University of Rome, Rome, Italy

Keywords
COVID-19 · Hematological diseases · Prevalence · Infection control

Abstract
Introduction: Patients with cancer may be more susceptible to and have higher morbidity and mortality rates from COVID-19 than the general population, while epidemiologic data specifically addressed to hematologic patients are limited. To investigate whether patients with hematologic diseases undergoing therapy are at increased risk for acquiring SARS CoV-2 infection compared to the general population, a retrospective study was carried out at a referral hematologic center in Rome, Italy, during the period of the greatest epidemic spread (March 8 to May 14, 2020). ***Methods:*** All adult and pediatric patients with a diagnosis of a neoplastic or a nonneoplastic hematologic disease who underwent treatment (chemotherapy or immunosuppressive or supportive therapy) during the study period or in the previous 6 months were considered. The prevalence of COVID-19 in the overall outpatient and inpatient population undergoing hematologic treatment compared to that of the general population was analyzed. The measures taken to manage patients during the epidemic period are described. ***Results:*** Overall, 2,513 patients with hematological diseases were considered. Out of 243 (9.7%) patients who were screened for SARS CoV-2, three of 119 (2.5%) outpatients with fever or respiratory symptoms and none of 124 asymptomatic patients were diagnosed with COVID-19. Three further patients were diagnosed with COVID-19 and managed in other hospitals in Rome. As of May 14, 2020, the prevalence of COVID-19 in our hematologic population accounted for 0.24% (95% CI 0.23–0.25; 6 of 2,513 patients: 1 case in every 419 patients) as compared to 0.12% (7,280 of 5,879,082 residents; 1 case in every 807 residents) in the general population ($p = 0.14$). Three of

karger@karger.com
www.karger.com/aha

Corrado Girmenia
Hematology, Department of Hematology, Oncology and Dermatology
AOU Policlinico Umberto I, Sapienza University of Rome
IT–Rome (Italy)
girmenia@bce.uniroma1.it

6 patients diagnosed with COVID-19 required critical care and 2 died while still positive for SARS CoV-2. Out of 225 healthcare providers on duty at our Institution during the study period, 2 (0.9%) symptomatic cases were diagnosed with COVID-19. ***Conclusion:*** In our experience, the prevalence of COVID-19 in hematologic patients, mainly affected by malignancies, was not significantly higher compared to that of the general population. Definition of adapted strategies for healthcare services, while continuing to administer the standard hematologic treatments, represents the crucial challenge for the management of hematologic diseases in the COVID-19 era.

Introduction

The world is experiencing a pandemic of coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Starting on March 8, 2020, the Italian Government adopted new measures to contain the epidemiologic COVID-19 emergency in the so-called red areas and throughout the country. In Italy, 222,074 confirmed cases and 29,692 deaths have been registered as of May 14, 2020, in SARS-CoV-2+ individuals [2]. The morbidity and mortality of this infection increase with the increasing age of the population. The median age of COVID-19 cases in Italy is 62 years, and in particular in the Italian region Lazio it is 57 years [3].

Available data seem to show that patients with cancer may be more susceptible and have higher morbidity and mortality rates from COVID-19 than the general population [4–9]. However, these estimates are controversial and it is unclear if this increased risk applies to patients with hematologic malignancies. One might hypothesize that also patients with hematologic diseases, particularly those undergoing chemotherapy, stem cell transplant, or other immunosuppressive treatments, would be at increased risk of SARS-CoV-2 infection. However, it is striking that this population appears to be poorly represented in the comorbidities reported for patients with COVID-19. Indeed, epidemiologic data specifically regarding hematologic patients are limited [10–13].

A further challenging issue is represented by prevention and management of the infection as well as the safe and timely administration of hematologic therapy, considering that guidelines for the management of hematologic patients in the current SARS-CoV-2 outbreak are not evidence based [14–27].

Herein, we report the experience at a large referral adult and child hematology center in Rome, Italy, with an analysis of the prevalence of COVID-19 in the overall outpatient and inpatient population undergoing hematologic treatment compared to that of the general population. The measures taken to manage patients during the period of the greatest spread of the epidemic are described.

Patients and Methods

Starting on March 8, 2020, a wide information campaign addressed to patients and healthcare personnel was carried out at our center according to the operative instructions for the management of the SARS CoV-2 pandemic indicated by the national government and by the General Manager of the AOU Policlinico Umberto I. Information regarded the epidemiologic control strategy and detailed operating instructions for preventing the spread of the infection.

This is an observational study performed at the Hematology Center of the AOU Policlinico Umberto I, Sapienza University of Rome, Italy. Patients' data were obtained by reviewing the medical records of patients followed during the period from March 8 to May 14, 2020.

The inclusion criteria were as follows:

- Adult and pediatric patients with a diagnosis of a neoplastic or non-neoplastic hematologic disease undergoing treatment (chemotherapy or immunosuppressive or supportive therapy) during the study period or in the previous 6 months; patients in disease remission and off-therapy for over 6 months before March 8, 2020; and patients with chronic hematologic diseases not requiring any treatment (watch and wait strategy) were not considered because the epidemiologic analysis would have been unreliable for the risk of underestimation. Many of these patients were never visited or contacted during the study period.
- Patients who were not visited at our center during the study period but who underwent a telemedicine visit (telephone or web contact) were also considered. Outpatients and their relatives followed at our Center have always been instructed to inform the reference hematologist of any relevant health event.

The procedures for the care of patients attending our center were carried out as follows:

- Outpatient visits: those deemed deferrable were postponed. When appropriate and feasible, visits were substituted with telemedicine. Nondeferrable outpatient visits were scheduled by appointment, defining contact prevention and hygiene procedures (crowding in waiting rooms was avoided, patients possibly waited outside the hospital [i.e. in their car], and patients and healthcare professionals were instructed to use protective masks and wash and/or disinfect hands with alcohol solutions). Patients entered the room for the visit without being accompanied, when possible. The administration of therapies (i.e., chemotherapy, immunotherapy, and blood product transfusion) in the day hospital was regulated with the above procedures.
- Hospital admission: on the day prior to hospitalization all of the patients underwent a nasopharyngeal swab for the detec-

Table 1. Characteristics of the population of patients with hematologic diseases undergoing active or supportive treatment followed at the Hematology Center of the AOU Policlinico Umberto I, Sapienza University, during the period of March 8 to May 14, 2020

Underlying disease or condition	Total patients, *n*	Male/female ratio	Age (<20/20–60/>60), years	Documented COVID-19 cases, *n*
Acute myeloid leukemia	79	34/45	5/16/58	0
Myelodysplastic syndromes	196	115/81	0/14/182	1
Chronic myeloid leukemia	303	140/163	15/157/131	0
Other myeloproliferative neoplasms	646	278/368	17/222/407	1
Acute lymphoid leukemia	69	31/38	30/20/19	0
Multiple myeloma	173	93/80	0/50/123	0
Amyloidosis	4	2/2	0/0/4	0
Non-Hodgkin lymphoma	283	138/145	7/72/204	3
Hodgkin lymphoma	72	40/32	14/48/10	0
Chronic lymphocytic leukemia	160	54/106	0/54/106	0
Hairy cell leukemia	6	5/1	0/4/2	0
Other lymphoproliferative diseases	7	4/3	2/2/3	0
Histiocytosis	64	40/24	41/15/8	0
Aplastic anemia and other bone marrow failures	23	10/13	6/13/4	0
Paroxysmal nocturnal hemoglobinuria	21	11/10	0/18/3	0
Thalassemia	106	54/52	10/94/2	1
Other hereditary anemias	42	20/22	28/13/1	0
Thrombotic thrombocytopenic purpura	7	2/5	4/2/1	0
Idiopathic thrombocytopenic purpura	97	39/58	24/31/42	0
Autoimmune hemolytic anemia	53	22/31	14/12/27	0
Gaucher disease	29	14/15	16/11/2	0
Acquired hemophilia	7	3/4	0/5/2	0
Allogeneic stem cell transplant	66	28/38	5/48/13	0
Total	2,513	1,177/1,336	238/921/1,354	6

Patients with a chronic hematologic disease not receiving any treatment and those off therapy for more than 6 months were not included.

tion of SARS-CoV-2 and negative patients entered the ward after an appropriate triage to rule out fever or respiratory signs and symptoms. Virologic testing and triage were also performed to caregivers accompanying children. If an urgent hospitalization was necessary, the patient stayed in an isolation area while waiting for the virology report. After the hospitalization, a careful surveillance of inpatients was also implemented in order to detect nosocomial cases of COVID-19. Patient visits were limited to 1 visitor per day per patient.

- Management of outpatient complications: outpatients were instructed to refer to a dedicated H24 Hematologic Emergency Unit (HEU) of our Center in the event of any type of complication. All patients with a fever or respiratory symptoms were tested for SARS CoV-2, underwent laboratory, radiologic, and physical exams as appropriate, and were placed in an isolation area until the results of the virologic exams were available. Also patients asymptomatic at the time of HEU admission but who reported the above clinical findings in the previous days were managed as above. In the event of a documented SARS CoV-2 infection the patient was transferred to the COVID unit of the hospital.
- Home care: a home care service (HCS) dedicated to patients with advanced hematologic diseases requiring palliative care and also patients eligible for active therapy but with a physical disability that makes nonhome management difficult is available at out center. During the COVID-19 pandemic the activity of the HCS continued regularly and new patients were enrolled. The above described contact prevention and hygiene procedures for patients, cohabitants, and HCS staff were applied at the patient's home.

During the study period, while applying the above infection control procedures, we decided not to change the standard treatment strategies, including intensive chemotherapy and stem cell transplant.

The aim of this study was to describe the prevalence of documented COVID-19 in the adult and pediatric populations affected by a hematologic disease undergoing active therapy followed at our center compared to that of the general population of the Lazio region [2, 3]. The number of residents in the Lazio region (as of January 2020) was extracted from the data of the Italian National Statistics Institute (ISTAT; Istituto Nazionale di Statistica) (www.dati.istat.it). The cases of COVID-19 documented in the Lazio region as of May 14, 2020, were extracted by the report of the Italian National Institute of Health (ISS; Istituto Superiore di Sanità) [3].

Patients were stratified according to the underling hematologic disease, gender, and age (<20, 20—59, and >60 years). Detailed

demographic and disease data were collected for the cases of COVID-19 documented during the study period. A case of COVID-19 was defined by the detection of a SARS CoV-2 RNA-specific fragment by real-time reverse transcriptase polymerase chain reaction (RT-PCR) (RealStar SARS-CoV-2 RT-PCR; Altona Diagnostics, Hamburg, Germany) from a nasopharyngeal swab. Groups were compared using a 2-tailed Fisher exact test.

Results

Overall, 2,513 patients with hematologic diseases fulfilling the above inclusion criteria were considered (Table 1). They included all patients who attended the ambulatory service (in person or by telemedicine), were referred to the HEU, were followed at home by the HCS, and were hospitalized during the study period. Of these, 116 (4.6%) outpatients with fever or symptoms compatible with a respiratory infection who attended the HEU underwent 127 SARS CoV-2 exams (1, 2, and 3 exams in 106, 9, and 1 patient, respectively); in 3 cases a diagnosis of COVID-19 was made and the patients were transferred to the COVID-19-dedicated unit of our hospital. Another 3 of our patients were diagnosed with COVID-19 and managed in other hospitals in Rome. None of the 66 outpatients followed at home by the HCS was diagnosed with COVID-19 (the virologic exam was performed in 3 patients with suspicion of infection). No case of COVID-19 was documented during hospitalization in 124 patients admitted to the wards of our center for the treatment of hematologic diseases during the study period (164 virologic exams; in all patients, the virologic exam was performed at the time of hospital admission and in 36 patients it was repeated during the hospitalization as indicated). Overall, 3 of 119 (2.5%) outpatients with fever or respiratory symptoms screened for SARS CoV-2 (at our HEU or by the HCS) and none of the 124 asymptomatic patients screened prior to hospital admission were diagnosed with COVID-19. All 19 screened caregivers accompanying children had negative test results.

As of January 2020, the population in the Lazio region was 5,879,082 people (1,053,165 aged <20 years; 3,179,552 aged 20–59 years; and 1,646,365 aged ≥60 years). As of May 14, 2020, the prevalence of COVID-19 in our hematologic population accounted for 0.24% (95% CI 0.23–0.25; 6 of 2,513 patients: 1 case in every 419 patients), compared to 0.12% (7,280 of 5,879,082 residents; 1 case in every 807 residents) in the general population (p = 0.14). The prevalence of COVID-19 was 0% (0 of 223) in our patients aged <20 years compared to 0.03% (295 of 1,053,165) in the general population (p = 1), 0.32% (3 of 936) in our patients aged 20–59 years compared to 0.11% (3,647 of 3,179,552) in the general population (p = 0.09), and 0.22% (3 of 1354) in our patients aged ≥60 years compared to 0.20% (3,335 of 1,646,365) in the general population (p = 1).

The characteristics of the 6 patients with a confirmed diagnosis of COVID-19 are reported in Table 2. Three of them required critical care for COVID-19 symptoms and 2 died while still positive for SARS CoV-2.

Out of 225 healthcare providers on duty at our center during the study period, 2 (0.9%) symptomatic cases (a nurse and a doctor who were cohabitants) were diagnosed with COVID-19 and all additional 25 asymptomatic healthcare providers screened for SARS CoV-2 due to close contact with COVID-19 proved negative.

Discussion

In this study, we analyzed the prevalence of COVID-19 in patients with hematologic diseases receiving active and/or supportive treatment. The only data reported in the literature to date on the epidemiology of the COVID-19 in large hematologic populations of patients are represented by 3 Italian surveys which showed a prevalence of 0.4% (1 of 267 patients) in adult Ph+ acute lymphoblastic leukemia patients, 0.5% (47 of 9,339 patient) in chronic lymphocytic leukemia patients, and 0.17% (12 of 6,883 patients) in chronic myeloid leukemia patients, and a Chinese study from the Hubei province on 530 subjects with chronic myeloid leukemia which reported a prevalence of 0.9% that was 9-fold higher than normal but much lower than the prevalence in hospitalized patients with other cancers or normal healthcare providers [10–13]. No information is available on childhood hematologic cancer populations.

We found that the prevalence of COVID-19 in our hematologic patients, mainly affected by malignancies, was not significantly higher compared to that in the general population. Only 2.5% (3 of 119) of our symptomatic patients screened for SARS CoV-2 were diagnosed with COVID-19. The prevalence of the disease in healthcare providers was 0.9% and, as in our patients, no positivity was found among asymptomatic subjects. These data should be evaluated with caution in view of the following considerations. First, an underestimation of the SARS CoV-2 epidemiology in the general population is more likely than in high-risk subpopulations, such as those affected by hematologic diseases, usually submitted to strict monitoring of any type of infective complication. Indeed,

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Table 2. Epidemiologic and clinical characteristics of 6 patients with a confirmed SARS-CoV-2 infection

Age, years/sex:	Patient 1 56/M	Patient 2 93/F	Patient 3 38/M	Patient 4 65/F	Patient 5 80/M	Patient 6 46/M
History of contact with an infected person	Hospital acquired infection; the patient was hospitalized in an internal medicine department where a COVID-19 outbreak occurred	The patient was resident in a home care facility for elderly where a COVID-19 outbreak occurred	Local COVID-19 outbreak in the neighborhood where he was resident	No	Hospital acquired infection; The patient was hospitalized in a rehabilitation hospital where a COVID-19 outbreak occurred	Dinner with person with subsequent COVID-19 diagnosis
Other family members affected	No	No	No	No	No	No
Hematologic disease and disease phase (date of diagnosis)	Post-essential thrombocythemia myelofibrosis with osteosclerosis (2010)	Low risk myelodysplastic syndrome (2012)	Non-Hodgkin lymphoma at onset (February 2020)	Relapsed non-Hodgkin lymphoma (onset in 2013, relapse in October 2018)	Non-Hodgkin lymphoma in partial remission (2003)	Thalassemia major
Comorbidities	Recent splenectomy complicated by thrombosis of the portal vein and myocarditis	No	No	Recent pulmonary infection by atypical mycobacteria	Chronic obstructive pulmonary disease with recurrent infections; chronic renal failure; recent femur fracture	Splenectomy
Therapy history of the hematologic disease; type and date of the last therapy	Anagrelide (from 2010 to 2014), ruxolitinib (from October 2017 to June 2019); the patient was an allogeneic stem cell transplant candidate	Erythropoietin therapy and blood transfusions within 5 years	1st cycle of R-CHOP on February 25, 2020	Chemotherapy. (rituximab plus bendamustine followed by R-CHOP, last cycle on April 20, 2020)	Last chemotherapy in 2015 (rituximab plus bendamustine); under steroid therapy	Transfusions Chelation therapy
Date of the first positive RT-PCR test (time from the onset of symptoms to diagnosis)	March 28, 2020 (4 days)	April 7, 2020 (2 days)	March 9, 2020 (7 days)	April 23, 2020 (1 days)	April 27, 2020 (7 days)	March 13, 2020 (7 days)
Signs and symptoms at diagnosis	Fever, respiratory failure	Mild fever	Fever, dry cough	Fever, dry cough	Fever, dry cough, abdominal pain related to cholecystitis	Fever and dyspnea
Site of patient care for COVID-19	Intensive care unit	Infectious disease department	Infectious disease department	Infectious disease department	Infectious disease department	Infectious disease department
Evolution of signs and symptoms, complications	Worsening of the respiratory failure, extensive -thrombosis of the intra-abdominal vessels	Rapid defervescence; the patient was hospitalized mainly for isolation	Fatigue, dyspnea, pneumonia	Dyspnea, respiratory failure	Stable clinical conditions; cholecystectomy	Pneumonia and pulmonary embolism
Chest computed tomography scan findings	Bilateral interstitial pneumonia	No pulmonary infiltrates	Bilateral interstitial pneumonia	Bilateral interstitial pneumonia	Mild ground-glass opacities	Bilateral interstitial pneumonia
Blood routine		NA				
Leukocytes, n/mm^3	42,940		3,690	1,660	5,000	9,420
Neutrophils, n/mm^3	18,130		2,970	1,320	3,650	4,970
Lymphocytes, n/mm^3	9,180		500	270	960	3,550
Platelets, n/mm^3	12,000		401,000	214,000	143,000	694,000
Hemoglobin, g/dL	8.2		14.3	8.6	9.8	11.3

Table 2 (continued)

Age, years/sex:	Patient 1 56/M	Patient 2 93/F	Patient 3 38/M	Patient 4 65/F	Patient 5 80/M	Patient 6 46/M
Coagulation function		NA		NA		
APTT	Ratio 1.12		Ratio 0.98		Ratio 0.83	Ratio 1.02
PT	Ratio 1.36		Ratio 0.95		Ratio 1.08	Ratio 1.12
D-dimer	13,920 μg/L		1,545 μg/L		1,180 μg/L	565 μg/L
Physiotherapy and medicine therapy	CPAP, endotracheal intubation	No specific antiviral therapy, no respiratory support	Lopinavir/ritonavir, hydroxichloroquine, azithromycin, and tocilizumab; oxygen therapy with a mask	Lopinavir/ritonavir, hydroxychloroquine, azithromycin, and tocilizumab; CPAP	Entecavir, hydroxychloroquine, and azithromycin; oxygen therapy with a mask	Lopinavir/ritonavir,
First negative RT-PCR test, days from the diagnosis	Patient died while still positive	15	14	Patient died while still positive	7	19
Outcome	Progression, patient died	Resolved	Resolved	Progression, patient died	Still hospitalized, stable general condition	Resolved

NA, not available; M, male; F, female.

our high-risk population underwent closer monitoring than the rest of the population who, according to the national government provisions, was not subjected to an intensive diagnostic strategy, particularly in the presence of mild symptoms. At least 10% of our patients underwent a virologic exam during the study period, compared to the less than 1% estimated in the population of the Lazio region. Second, the incidence of documented COVID-19 in the Lazio region was not particularly high and a similar study carried out in areas with a greater epidemic impact would provide different results. Third, 3 of the 6 patients diagnosed with COVID-19 acquired the viral infection in other hospitals or in long-term care facilities where local outbreaks were documented.

The suggested basic protective measures against COVID-19 – i.e., frequent hand washing and disinfection, social distancing, avoiding crowded places, and keeping distance with anyone who is coughing or sneezing – have always been advised to our patients particularly during the periods of higher risk after immunosuppressive treatments. This could be a possible explanation for the contained spread of COVID-19 observed in our hematologic patients despite the scheduled treatment, including intensive chemotherapy and stem cell transplant. Probably, at the beginning of the epidemic, when preventive measures had not yet been disclosed, these historic measures protected our patients from the risk of acquiring the SARS CoV-2 infection. It is also worth noting that our hematology center is detached from the main hospital. This has clearly limited the risks of infections associated with a large multidisciplinary hospital.

Another important issue is represented by the risk of developing more serious SARS CoV-2 infections with a higher mortality than in nonhematologic populations. In our experience, 3 out of 6 patients were in critical care and 2 of them died with persistent positive SARS-CoV-2, but both patients suffered from a very advanced hematologic disease with a long disease history and severe comorbidities. Studies in cancer populations have reported that COVID-19 in adult patients with solid tumors has higher rates of severe illness (intensive care unit admissions, invasive ventilation, or death) compared to others, and logistic regression has identified cancer as the highest individual risk factor for severe events (OR = 5.4; 95% CI1.8–16.2; $p = 0.003$) [4–7]. In the childhood population, cancer does not appear to be a condition that worsens the SARS CoV-2 infection outcome; in a study on 20 cancer children with COVID-19 most patients had mild symptoms and were managed at home and only 1 required noncritical care hospitalization for COVID-19 symptoms [8].

There are few data on the clinical evolution of COVID-19 in patients with hematologic diseases as mainly case reports have been reported so far [28–39]. In a cohort study at 2 centers in Wuhan, China, hospitalized persons with hematologic cancers had a similar case rate of COVID-19 (10%) compared to normal healthcare providers (7%), but they had more severe disease and a higher case fatality rate (62 vs. 0%) [36]. However, this study has important limitations including the heterogeneous patient population, hematologic diagnoses and disease states, confounding covariates such as therapy of hematologic cancers, hospitalization, and interval to developing COVID-19; therefore, the independent role of the underlying malignancy in the evolution of the viral disease could not be documented.

Due to the lack of good-quality data, the question of how to manage hematologic diseases, in particular malignancies, during the COVID-19 pandemic is a challenging issue, even if some not-evidence-based indications have been addressed by scientific societies and opinion leaders [14–27]. A risk-benefit evaluation should consider, on the one hand, that patients may be at a high risk of contracting the infection and dying from it and, on the other hand, that patients may be at a high risk of a fatal hematologic disease progression if not treated appropriately and timely. With the aim of reducing the risk of patient exposition to the viral infection, alternative strategies could be considered while waiting for scientific evidence, i.e., telemedicine services; a reduction of clinic visits; less intensive chemotherapy and immunotherapy regimens; switch to subcutaneous or oral therapies, rather than intravenous ones, when possible; and postponement of stem cell transplant procedures to a more favorable epidemic phase. Based on our institutional experience during the 2 months of the greatest spread of the epidemic in Italy, in which all our organizational care strategies were modified in view of the COVID-19 phenomenon while administration of the standard hematologic treatments was continued, we suggest not changing the treatment strategies of the hematologic diseases and implementing infection control models in the overall patient management. Definition of adapted strategies for healthcare services, including new rules for hospital admission, alternative models of outpatient visits, and dedicated routes for the emergencies of outpatients, represents the crucial challenge for the management of hematologic diseases in the COVID-19 era. A further clinical problem is represented by the interpretation of laboratory data in patients with COVID-19 and an underlying blood disease. Systemic COVID-19 could have a significant impact on the hematopoietic system and hemostasis [40]. Lymphopenia, elevation of inflammatory indices, and coagulation abnormalities are common among hospitalized COVID-19 patients; however, interpretation of these laboratory alterations may be difficult in hematologic patients receiving chemotherapy or immunotherapy. Our 6 patients with COVID-19 showed no particular changes in laboratory parameters at onset and during the viral infection.

The treatment of patients with COVID-19 deserves some comments. Many clinical trials are underway to investigate the efficacy of vaccines and various antiviral therapies targeting SARS-CoV-2, but the inclusion of patients with hematological malignancies in these trials is variable [41]. Preliminary data suggest that convalescent plasma or concentrated hyperimmune globulin preparations might be beneficial either for prophylaxis of infection or the treatment of COVID-19 [42, 43], and the case of a patient with follicular lymphoma who endured a protracted course of COVID-19 and rapidly responded after a single 200-mL COVID-19 convalescent plasma infusion was reported [44]. None of our patients was treated with convalescent plasma as this treatment is allowed only in the context of clinical trials in Italy. At the moment there are insufficient data to give specific indications for the prophylaxis and treatment of SARS-CoV2 infection and disease in hematological patients; however, it is reasonable to consider convalescent plasma in patients with a severe viral disease and known B-cell deficiency with hypogammaglobulinemia.

Statement of Ethics

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, it was approved by the institutional review board, and informed consent for the use of clinical data for scientific purposed has been obtained from all patients. Each case of confirmed COVID-19 was reported to the local and regional Epidemiologic Infection Control Service. This is a noninterventional cohort study and collection and storage of data were performed by the investigators directly involved in the patients' care using current techniques of ensuring privacy; ethics committee approval was, therefore, not necessary.

Conflict of Interest Statement

All of the authors declare no conflict of interests.

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Author Contributions

All of the authors contributed to the research design or the acquisition, analysis, or interpretation of data. The submitted, final version of this paper was approved by all of the authors. C. Girmenia, M. Martelli, G. Gentile, and A. Micozzi designed and performed this research study. C. Girmenia, G. Gentile, and A. Micozzi analyzed the data. C. Girmenia, G. Gentile, A. Micozzi, M. Martelli, and R. Foà wrote this paper.

Institutional Study Participants

- Myeloproliferative diseases team: Massimo Breccia, Roberto Latagliata, Marco Mancini, Erminia Scalzulli, Alessio Di Prima, Cristina Scamuffa, Gioia Colafigli, Sara Pepe.
- Lymphoproliferative diseases team: Maurizio Martelli, Alice Di Rocco, Alessandro Pulsoni, Giannamaria D'Elia, Francesca Romana Mauro, Maria Teresa Petrucci, Sabina Chiaretti, Ilaria Del Giudice, Antonella Vitale, Luigi Petrucci, Francesco Malaspina, Costantino Riemma, Laura Ballotta, Giulia De Luca, Gianfranco Lapietra, Francesca Fazio, Giacomo Maestrini, Silvio Ligia, and Marika Porrazzo.
- Hemorrhagic and thrombotic diseases team: Antonio Chistolini, Cristina Santoro, Erminia Baldacci, Francesco Dragoni, Alessandra Serrao, Antonietta Ferretti, Luciano Fiori, and Rebecca Poggiali.
- Allogeneic stem cell transplant team: Anna Paola Iori, Walter Barberi, Ursula La Rocca, Luisa Quattrocchi, Roberta Agrippino, Maria Assunta Limongello, Paolo Musiu, and Roberto Ricci.
- General hematology team: Stefania Trasarti, Maria Luisa Bizzoni, Marco Vignetti, Cristina Luise, and Maria Laura Bisegna.
- Hematology wards team: Saveria Capria, Maria Silvia Trisolini, Clara Minotti, Fabiana Gentilini, Giovanni Assanto, Francesca Kaiser, Giulia Ciotti, Germana Tartaglia, Federica Viola, and Laura Cesini.
- Hematologic emergency unit team: Corrado Girmenia, Salvatore Giacomo Morano, Gregorio Antonio Brunetti, Mattia Brescini, and Chiara Lisi.
- HCS team: Claudio Cartoni, Ida Carmosino, Giovanna Palumbo, and Giorgia Annechini.
- Pediatric team: Anna Testi, Maria Luisa Moleti, Francesco Malfona, Simona Bianchi, and Francesca Paoletti.
- Rare diseases team: Fiorina Giona, Daniela De Benedittis, Sara Mohamed, and Luisa Cardarelli.
- Thalassemia team: Pellegrina Pugliese, Marco Marziali, Michela Ribersani, and Anna Annunziata Losardo.
- Infection control team: Giuseppe Gentile and Alessandra Micozzi.
- Radiology team: Simonetta Brocchieri.
- Hematology laboratory team: Anna Rita Guarini, Maria Stefania De Propris, Francesca Mancini, Maria Grazia Nardacci, Daniela Diverio, Loredana Elia, and Mauro Nanni.
- Laboratory of virology team: Guido Antonelli, Ombretta Turriziani, Francesca Falasca, Massimo Gentile, Valeria Pietropaolo, Ilaria Sciandra, and Donatella Rodio.

References

1 World Health Organization. Coronavirus. Available from: https://www.who.int/health-topics/coronavirus#tab=tab_1.
2 Istituto Superiore di Sanità. Epidemia COVID-19: aggiornamento nazionale. Available from: https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_14-maggio-2020.pdf.
3 Istituto Superiore di Sanità. Aggiornamento nazionale (appendice). Available from: https://www.epicentro.iss.it/coronavirus/bollettino/Bolletino-sorveglianza-integrata-COVID-19_14-maggio-2020_appendix.pdf.
4 Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020 Mar;21(3):335–7.
5 Zheng RS, Sun KX, Zhang SW, Zeng HM, Zou XN, Chen R, et al. Report of cancer epidemiology in China, 2015. Zhonghua Zhong Liu Za Zhi. 2019 Jan;41(1):19–28.
6 Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for patients with cancer. Lancet Oncol. 2020 Apr;21(4):e180.
7 Yu J, Ouyang W, Chua ML, Xie C. SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China. JAMA Oncol. 2020 Mar;6(7):e200980.
8 Boulad F, Kamboj M, Bouvier N, Mauguen A, Kung AL. COVID-19 in children with cancer in New York City. JAMA Oncol. 2020. doi: 10.1001/jamaoncol.2020.2028.
9 Hrusak O, Kalina T, Wolf J, Balduzzi A, Provenzi M, Rizzari C, et al. Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anticancer treatment. Eur J Cancer. 2020 Jun;132:11–6.
10 Foà R, Bonifacio M, Chiaretti S, Curti A, Candoni A, Fava C, et al. Ph+ acute lymphoblastic leukaemia in Italy during the Covid-19 pandemic: a Campus ALL study. Br J Haematol. 2020 Jul;190(1):e3–e5.
11 Cuneo A, Scarfò L, Reda G, Varettoni M, Quaglia FM, Marchetti M. et al. Chronic lymphocytic leukemia management in Italy during the covid-19 pandemic: a Campus CLL report. Blood. 2020. doi: 10.1182/blood.2020006854.
12 Breccia M, Abruzzese E, Bocchia M, Bonifacio M, Castagnetti F, Fava C, et al.; Campus CML working group. Chronic myeloid leukemia management at the time of the COVID-19 pandemic in Italy. A campus CML survey [Online ahead of print.]. Leukemia. 2020 Aug;34(8):2260–1.
13 Li W, Wang D, Guo J, Yuan G, Yang Z, Gale RP, et al.; Hubei Anti-Cancer Association. COVID-19 in persons with chronic myeloid leukaemia. Leukemia. 2020 Jul;34(7):1799–804.
14 Ueda M, Martins R, Hendrie PC, McDonnell T, Crews JR, Wong TL, et al. Managing Cancer Care During the COVID-19 Pandemic: Agility and Collaboration Toward a Common Goal [Online ahead of print.]. J Natl Compr Canc Netw. 2020 Mar;1-4(4):1–4.
15 Cinar P, Kubal T, Freifeld A, Mishra A, Shulman L, Bachman J, et al. Safety at the Time of the COVID-19 Pandemic: How to Keep our Oncology Patients and Healthcare Workers Safe [Online ahead of print.]. J Natl Compr Canc Netw. 2020 Apr;18(5):1–6.
16 Falandry C, Filteau C, Ravot C, Le Saux O. Challenges with the management of older patients with cancer during the COVID-19 pandemic. J Geriatr Oncol. 2020 Jun;11(5):747–9.
17 Gavillet M, Carr Klappert J, Spertini O, Blum S. Acute leukemia in the time of COVID-19. Leuk Res. 2020 Mar;92:106353.
18 Raza A, Assal A, Ali AM, Jurcic JG. Rewriting the rules for care of MDS and AML patients in the time of COVID-19. Leuk Res Rep. 2020;13:100201.

19 Perini GF, Fischer T, Gaiolla RD, Rocha TB, Bellesso M, Teixeira LL, et al.; Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular (ABHH). How to manage lymphoid malignancies during novel 2019 coronavirus (CoVid-19) outbreak: a Brazilian task force recommendation. Hematol Transfus Cell Ther. 2020 Apr - Jun;42(2):103–10. ; Epub ahead of print.
20 von Lilienfeld-Toal M, Vehreschild JJ, Cornely O, Pagano L, Compagno F, Hirsch HH; EHA Infectious Disease Scientific Working Group. Frequently asked questions regarding SARS-CoV-2 in cancer patients-recommendations for clinicians caring for patients with malignant diseases. Leukemia. 2020 Jun; 34(6):1487–94. ; Epub ahead of print.
21 Paul S, Rausch CR, Jain N, Kadia T, Ravandi F, DiNardo CD, et al. Treating leukemia in the time of COVID-19. Acta Haematol. 2020. doi: 10.1159/000508199.
22 Ljungman P, Mikulska M, de la Camara R, Basak GW, Chabannon C, Corbacioglu S, et al.; European Society for Blood and Marrow Transplantation. The challenge of COVID-19 and hematopoietic cell transplantation: EBMT recommendations for management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy. Bone Marrow Transplant. 2020. doi: 10.1038/s41409-020-0919-0.
23 Patnaik MM, Lasho T, Padron E, McCullough K, Al-Kali A, Tefferi A, et al. Special considerations in the management of patients with myelodysplastic myndrome / myeloproliferative neoplasm overlap syndromes during the SARS-CoV-2 pandemic. Am J Hematol. 2020 Aug;95(8):E203–8. ; Epub ahead of print.
24 Burki TK. Cancer guidelines during the COVID-19 pandemic. Lancet Oncol. 2020 May; 21(5):629–30.
25 Gale RP. Perspective: SARS-CoV-2, COVID-19 and haematologists. Acta Haematol. 2020 May;1–4:1–4.
26 Terpos E, Engelhardt M, Cook G, Gay F, Mateos MV, Ntanasis-Stathopoulos I, et al. Management of patients with multiple myeloma in the era of COVID-19 pandemic: a consensus paper from the European Myeloma Network (EMN) [published online ahead of print, 2020 May 22]. Leukemia. 2020 Aug;34(8):2000–11.
27 Sullivan M, Bouffet E, Rodriguez-Galindo C, Luna-Fineman S, Khan MS, Kearns P, et al. The COVID-19 pandemic: a rapid global response for children with cancer from SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI, and St Jude Global. Pediatr Blood Cancer. 2020 Jul;67(7):e28409.
28 Zhang X, Song K, Tong F, Fei M, Guo H, Lu Z, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. Blood Adv. 2020 Apr;4(7): 1307–10.
29 Wu Y, Lin H, Xie Q, Chen Q, Huang Y, Zhu Y, et al. COVID-19 in a patient with pre-existing acute lymphoblastic leukaemia. Br J Haematol. 2020 Jul;190(1):e13–5. ; Epub ahead of print.
30 Treon SP, Castillo JJ, Skarbnik AP, Soumerai JD, Ghobrial IM, Guerrera ML, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. Blood. 2020 May;135(21):1912–5.
31 Paneesha S, Pratt G, Parry H, Moss P. Covid-19 infection in therapy-naive patients with B-cell chronic lymphocytic leukemia. Leuk Res. 2020 Jun;93:106366.
32 Jin XH, Zheng KI, Pan KH, Xie YP, Zheng MH. COVID-19 in a patient with chronic lymphocytic leukaemia. Lancet Haematol. 2020 Apr;7(4):e351–2.
33 Baldacini M, Pop R, Sattler L, Mauvieux L, Bilger K, Gantzer J, et al. Concomitant haemorrhagic syndrome and recurrent extensive arterial thrombosis in a patient with COVID-19 and acute promyelocytic leukaemia. Br J Haematol. 2020 Jun;189(6):1054–6. ; Epub ahead of print.
34 Sieni E, Pegoraro F, Casini T, Tondo A, Bortone B, Moriondo M, et al. Favourable outcome of coronavirus disease 2019 in a 1-year-old girl with acute myeloid leukaemia and severe treatment-induced immunosuppression. Br J Haematol. 2020 Jun;189(6):e222–4. ; Epub ahead of print.
35 Zhao Y, Zhao W, Wang A, Qian F, Wang S, Zhuang L, et al. First case of coronavirus disease 2019 in childhood leukemia in China. Pediatr Infect Dis J. 2020 Jul;39(7):e142–5.
36 He W, Chen L, Chen L, Yuan G, Fang Y, Chen W, et al. COVID-19 in persons with haematological cancers. Leukemia. 2020 Jun;34(6): 1637–45. ; Epub ahead of print.
37 Thibaud S, Tremblay D, Bhalla S, Zimmerman B, Sigel K, Gabrilove J. Protective role of BTK inhibitors in patients with chronic lymphocytic leukemia and COVID-19. Br J Haematol. 2020 Jul;190(2):e73–e76.
38 Baumann T, Delgado J, Montserrat E. CLL and COVID-19 at the Hospital Clinic of Barcelona: an interim report. Leukemia. 2020 Jul; 34(7):1954–6.
39 Farmer I, Okikiolu J, Steel M, Wanniarachchi C, Littlewood S, Gupta S, et al. Acute promyelocytic leukaemia lying under the mask of COVID-19-a diagnostic and therapeutic conundrum. Br J Haematol. 2020 May;190(4).
40 Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020 Jul;95(7): 834–47.
41 Zeidan AM, Boddu PC, Patnaik MM, Bewersdorf JP, Stahl M, Rampal RK et al. Special considerations in the management of adult patients with acute leukaemias and myeloid neoplasms in the COVID-19 era: recommendations from a panel of international experts. Lancet Haematol. 2020;S2352-3026(20) 30205-2.
42 Psaltopoulou T, Sergentanis TN, Pappa V, Politou M, Terpos E, Tsiodras S, et al. The Emerging Role of Convalescent Plasma in the Treatment of COVID-19. HemaSphere. 2020 May;4(3):e409.
43 Xia X, Li K, Wu L, hang Z, Zu M, Wang Bet al. Improved clinical symptoms and mortality on severe/critical COVID-19 patients utilizing convalescent plasma transfusion. Blood. 2020;136(6):755–75.
44 Wright Z, Bersabe A, Eden R, Cap A. Successful use of COVID-19 convalescent plasma in a patient recently treated for follicular lymphoma. Clin Lymphoma Myeloma Leuk. 2020;S2152-2650(20)30310-4.