

TO THE EDITOR:

Chronic lymphocytic leukemia management in Italy during the COVID-19 pandemic: a Campus CLL report

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Italy is one of the countries most severely affected by the COVID-19 outbreak. At the beginning of March 2020, health authorities issued rules to: (1) determine which patients and health personnel should be tested for COVID-19 infection by collection of a nasopharyngeal swab specimen; (2) limit access to hospitals for outpatient visits that could be postponed; and (3) regulate the access of personnel to laboratory activities. Our goal was to analyze the impact of these recommendations on the management of chronic lymphocytic leukemia (CLL), which is the leukemia with the highest prevalence in Western countries. We sent a questionnaire to 33 hematology centers in Italy during the first week of April 2020 addressing 3 different issues: (1) strategy for testing using nasopharyngeal swabs; (2) impact of the COVID-19 outbreak on the diagnosis, management, and outcome of patients with CLL; and (3) impact on adherence to clinical protocols. All centers were involved in the framework of the Campus CLL program ongoing in Italy. The centers are located throughout the entire territory and are following up on a regular basis at least 100 patients with CLL per center (range, 100-700; median, 200). Eighteen centers were based in northern Italy (north of Rome), the area most affected by the COVID-19 outbreak. This survey is based on 9930 patients with CLL managed during the COVID-19 pandemic, accounting for approximately one-third of all patients with CLL in Italy. The results are presented in Table 1 and invite some discussion.

Testing strategies for COVID-19 infection were not homogeneous throughout the country. The minimal bylaw requirement to test all patients with flu-like symptoms and/or who had been in close contact with a positive subject was enforced by all centers. Asymptomatic patients without any known contact were tested before treatment only in 30% of centers, a strategy that reflects the higher capacity of some regional health systems to perform and analyze nasopharyngeal swab specimens.

Overall, 47 symptomatic patients were found to be positive for COVID-19 as of 15 April 2020, in this cohort of 9330 patients with CLL followed up at the 33 centers (0.5%). The large majority of patients with COVID-19 came from the 4 regions most heavily affected by the pandemic: Lombardy, Piedmont, Veneto, and Emilia-Romagna. The centers involved in this survey are managing patients with CLL on a regular basis, and although some

COVID-19 cases may have been missed, the 0.5% prevalence recorded likely represents a relatively accurate estimate of the incidence of COVID-19 positivity in CLL in Italy. In one center, an active detection strategy was adopted by using telephone interviews to all patients with CLL, and no additional symptomatic cases were detected.

The prevalence of COVID-19 positivity in the 60.36 million inhabitants in Italy as of 15 April 2020, was 0.27% (data available at https://lab24.ilssole24ore.com/coronavirus/?utm_source=fasciahp#box_1), independent of age. It is worth noting that unlike our patients with CLL, many symptomatic individuals without coexisting conditions have so far not been routinely tested in Italy. These findings indicate that the overall prevalence of symptomatic COVID-19 cases of CLL is low and not significantly higher than that of the normal population despite the advanced median age of patients with CLL, the known associated immunosuppression, and the possible impact of treatment. This observation is in line with findings regarding Philadelphia-positive acute lymphoblastic leukemia,¹ in which the incidence increases with age, as well as in chronic myeloid leukemia,^{2,3} in which the median age is approximately 60 years.

With a few exceptions (3 of 33 centers), a triage is set up to identify symptomatic patients who are then tested in a dedicated area. The spaces are large enough to allow for adequate social distancing (ie, >1 m) in virtually all centers.

Because routine blood testing in peripheral laboratories has been discouraged, the majority of centers noted a lower incidence of newly diagnosed cases. Furthermore, a reduction in laboratory personnel has caused delays and difficulties in an accurate diagnostic evaluation and prognostic stratification of patients, a process of utmost importance for the correct management of CLL,^{4,5} in 15% of centers.

Our survey found that the COVID-19 outbreak has had an impact on treatment. We observed that: (1) treatment initiation was conducted without delay in only 21% of centers; (2) administration of ongoing treatment was delayed in 24% of centers, and in 1 center rituximab was suspended; (3) 45.5% of centers were advised to reduce use of blood product as much as possible due

Table 1. Impact of COVID-19 on the management of CLL in 33 Italian centers between March 3, 2020, and April 15, 2020

Question	No. (%) of centers
Testing for COVID-19	
Is asymptomatic health-care personnel tested for COVID-19 infection in the absence of known contact with COVID-19 patients?	
No	23 (70)
Yes	7 (21)
Yes, at least twice	3 (9)
Patients with CLL are tested using nasopharyngeal swabs	
Only if presenting with flu-like illness and/or close contact with a patient with COVID-19	23 (70)
As in situation above and before treatment administration	10 (30)
Patients admitted to the outpatient department for testing and/or visit and/or treatment	
Are screened for body temperature and flu-like symptoms before entrance	30 (91)
Are not screened before entrance	3 (9)
The spaces in the outpatient department are large enough to allow for social distancing (ie, >1 m) to be respected	
Yes	28 (85)
Yes, but the access of patients had to be rescheduled	2 (6)
No	3 (9)
Diagnosis and management of patients	
Did you notice in the last 40 d a reduction of newly diagnosed patients with CLL?	
Yes	20 (61)
No	13 (39)
Did you encounter problems in the diagnostic evaluation?	
Yes	5 (15)
No	28 (85)
PhD students and postdoctoral fellows involved in evaluation of patients with CLL	
Were admitted to the laboratories without restrictions	18 (55)
Were admitted with some limitations	10 (30)
Were not admitted at all	5 (15)
How were patients with both COVID-19 and CLL managed?	
Followed up on a daily basis at home by telephone if asymptomatic or with mild symptoms	26 (79)
Hospitalized independently of the presence of symptoms	7 (21)
Hospitalized patients were assigned	
To a dedicated COVID-19 ward	30 (91)
To dedicated single rooms in the hematology ward	3 (9)
Patients not on active CLL treatment who had a scheduled follow-up visit	
Were visited regularly	0 (0)
Were contacted by telephone, advised, and rescheduled	33 (100)
Patients with CLL progression requiring treatment according to the iwCLL criteria	
Started the planned treatment without delay	7 (21)
Start of treatment was postponed whenever possible	26 (79)
Patients who were on active CLL treatment	
Received the planned treatment without modifications (chemoimmunotherapy or oral agents)	24 (73)
Received the planned treatment, but the anti-CD20 monoclonal antibody was not administered	1 (3)
Postponed the scheduled course of chemoimmunotherapy	8 (24)
Patients who were scheduled for restaging during or posttherapy	
Were visited without delay	23 (70)
Were rescheduled >1 mo later	10 (30)
Use of blood or platelet transfusion	
Had no restriction	16 (48.5)
Had no restriction with an alert that donors were found to be positive for COVID-19 (not transmitted to the patient)	2 (6)
We were advised to reduce use of blood product as much as possible due to shortage of donors	15 (45.5)
Clinical trials	
Enrollment of patients with CLL in clinical trials (30 centers)	
Continued without significant modifications	10 (33)
We could not enroll patients because the CRO stopped accrual	10 (33)
We reduced our accrual potential for patient's or physician's choice	5 (17)
Problems in the follow-up of enrolled patients	5 (17)

CRO, contract research organization; iwCLL, International Workshop on Chronic Lymphocytic Leukemia.

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to a shortage of donors, and in 2 instances, donors were found to be positive for COVID-19, with no known impact on the patients; and (4) planned posttreatment restaging had to be postponed in 30% of the centers.

For the 46 patients with COVID-19 for whom we were able to collect clinical information, the infection occurred in both treated and untreated patients. More specifically, 16 patients with CLL had never been treated, 15 were receiving front-line or salvage treatment (5 on ibrutinib, 4 receiving chemoimmunotherapy, and 6 undergoing other treatments), 9 were within 6 months of stopping chemoimmunotherapy, and 6 had been treated earlier. Fourteen patients never required oxygen/ventilation, while 32 patients did. As of May 18, 2020, a total of 28 patients have fully recovered, 4 are in the hospital, 2 with noninvasive oxygen support, and 14 have died, with a mortality rate of 30.4% (median age, 75 years; range, 51-91 years). As of the same date, the mortality rate for symptomatic patients with COVID-19 among the general population in Italy was 13.4%, with 25.5% in the 70- to 79-year-old population (<https://www.epicentro.iss.it/coronavirus/>).

In a recent paper in *Blood*,⁶ it was hypothesized that ibrutinib, a Bruton tyrosine kinase inhibitor, may play a protective role against pulmonary injury in patients with COVID-19 and Waldenström macroglobulinemia. The authors were searching for further validation in other patient populations on ibrutinib treatment, namely CLL. So far, we could not associate the clinical course, aggressiveness, or outcome to the type of treatment, if any.

Finally, we investigated the level of enrollment of patients into a clinical trial or of adherence to the timing of ongoing protocols during the pandemic. In 33% of centers, there were no modifications in enrollment or follow-up of patients on protocol. However, contract research organizations stopped or slowed accrual in 33% of centers, there were no new enrollments due to the hematologist's decision or patient refusal in 17% of centers, and there were problems with follow-up visits of enrolled patients in 17% of centers.

Our survey on the management of CLL during the current pandemic allows some broader considerations. Thus far, patients with CLL seem to have been scarcely affected by COVID-19 during the outbreak and peak of the infection in Italy, irrespective of their median age, the associated immunosuppression, or treatment. Throughout the COVID-19 pandemic, patients have largely continued to be adequately managed. The numbers are too small to determine if the mortality in patients with both COVID-19 infection and CLL is higher than that of the normal population matched per age and if Bruton tyrosine kinase inhibitors may have a protective effect.

What is starting to emerge is an impact on the routine evaluation of patients, on treatment choices, and on the enrollment and adherence to clinical trials. Optimal management of patients with CLL requires extensive laboratory support in terms of diagnostic testing, genetic-based prognostic stratification, and monitoring of minimal residual disease. The survey has highlighted that these steps could not always be optimally guaranteed during the pandemic, which has started to affect the number of new cases, the adequate follow-up of treated patients, the number of patients enrolled in clinical trials, and the

monitoring of such patients. These factors will represent a major drawback in the overall management of CLL, as well as of other hematologic malignancies, should the pandemic not resolve rapidly.

Acknowledgments

The authors thank all the Campus CLL colleagues who completed the survey.

This study was partly supported by Associazione Italiana Ricerca sul Cancro, Special 5x1000 Program Metastases (21198), Milan, Italy (R.F.), and BEAT Leukemia (A.C.).

Authorship

Contribution: A.C. and R.F. planned and designed the survey, analyzed the data, and wrote the manuscript; L.S., G.R., M.V., F.M.Q., M.M., L.D.P., F.R., D.P., G.M.R., L.O., A.I., L.L., and R.M. contributed with clinical cases; and V.G., L.L., R.M., F.R.M., and L.T. discussed the survey and the results and reviewed the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

A complete list of the members of the the Campus CLL working group who completed the survey appears in "Appendix."

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Footnote

Requests for data sharing should be e-mailed to the corresponding author.

Appendix

The Campus CLL working group chairs are A.C. and R.F. and the working group coordinators are R.M., L.L., V.G., F.R.M., and L.T. The members who completed the survey include: Ilaria Angeletti (Azienda Ospedaliera Santa Maria di Terni, Terni, Italy), Federico Chiurazzi (Federico II University Medical School, Naples, Italy), Giovanni Del Poeta (Università Tor Vergata Roma, Rome, Italy), L.D.P. (University of Eastern Piedmont, Novara, Italy), Maria Rosaria De Paolis (PO Vito Fazzi, Lecce, Italy), Lucia Farina (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy), Angela Ferrari (Azienda USL-IRCCS, Reggio Emilia, Italy), V.G. (CRO, IRCCS, Aviano, Italy), Massimo Gentile (Azienda Ospedaliera di Cosenza, Cosenza, Italy), Daniela Gottardi (Ospedale Mauriziano, Turin, Italy), Alessandro Gozzetti (University of Siena, Siena, Italy), A.I. (Ospedale S. Martino, Genoa, Italy), L.L. (Fondazione Universitaria Policlinico A. Gemelli, Rome, Italy), Monica Leone (Azienda Villa Sofia-Cervello, Palermo, Italy), Luciano Levato (Azienda Ospedaliera Pugliese-Ciaccio, Cantanzaro, Italy), Monica Maccaferri (University of Modena and Reggio Emilia, Modena, Italy), Lara Malerba (Azienda Ospedaliera "Ospedali Riuniti Marche Nord," Pesaro, Italy), M.M. (Cardinal Massaia Hospital, Asti, Italy), F.R.M. (Sapienza University, Rome, Italy), Marina Motta (ASST Spedali Civili, Brescia, Italy), Roberta Murru (Ospedale A. Businco, Cagliari, Italy), Laura Nocilli (Ospedale Pardo, Messina, Italy), Jacopo Olivieri (Azienda Sanitaria Universitaria Integrata, Udine, Italy), L.O. (San Giovanni Battista Hospital, Turin, Italy), D.P. (Azienda Ospedaliera SS Arrigo e Biagio e Cesare Arrigo, Alessandria, Italy), F.M.Q. (University of Verona, Verona, Italy), F.R. (Azienda Ospedaliero Universitaria di Parma, Parma, Italy), G.R. (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy), G.M.R. (University of Ferrara, Ferrara,

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DOI 10.1182/blood.202006854

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TO THE EDITOR:

Red cell-bound antibodies and transfusion requirements in hospitalized patients with COVID-19

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The direct antiglobulin test (DAT) detects immunoglobulin or complement bound in vivo to red blood cells (RBCs) and is widely used to diagnose immune-mediated hemolytic anemias. Positive DAT results, with or without clinically evident anemia, have been reported in a subset of patients with various viral infections.¹ Very recently, a few cases with simultaneous onset of SARS-CoV-2 infection and autoimmune hemolytic anemia (AIHA) have been described.^{2,3}

During the first weeks of the coronavirus disease 2019 (COVID-19) outbreak, we noticed an increasing frequency of DAT positivity at the Blood Center of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan, Italy). Therefore, we studied samples from 113 consecutive patients with confirmed COVID-19 that were sent to our laboratory for pretransfusion testing and/or ABO and Rh typing during a single week (6-13 April 2020). All patients were hospitalized and receiving treatment with multiple drugs (including hydroxychloroquine, heparin, corticosteroids, anti-interleukin-1 biologicals, antivirals, antibiotics, vasopressors, and invasive or noninvasive ventilation). None of them received COVID-19 convalescent plasma. Red cell investigations were performed at the Immunohematology Reference Laboratory of the Department of Transfusion Medicine and Hematology of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, which is certified by the American Association of Blood Banks. The study was approved by the Institutional Review Board of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and conducted in accordance with the Declaration of Helsinki.

Red cell antibodies were determined by direct antiglobulin test and indirect antiglobulin test (IAT), using column agglutination technology (ORTHO BioVue system; Ortho Clinical Diagnostics,

Raritan, NJ) and polyspecific antiserum (immunoglobulin G [IgG] plus C3d) and specific antiserum (IgG). DAT reactivity was confirmed, and antibody specificity was determined by micro-column (IgG, IgA, IgM, C3c, C3d; DC-Screening I; Bio-Rad, Cressier, Switzerland). Reagent cells from patients and healthy donors were prepared from EDTA samples by washing the red cell fraction 3 times with saline. Specifically, we prepared 1 panel of 5DAT-negative patients with COVID-19 and 1 panel of 5 blood donors. A commercial panel of RBCs (SURGISCREEN; Ortho Clinical Diagnostics) was also used. Rapid acid elution (Gamma ELU-KIT II; Immucor Inc., Norcross, GA) was used for the recovery of antibodies bound to red cells, and the eluates were tested by IAT.

Fifteen consecutive samples were also tested by flow cytometry DAT. Briefly, packed RBCs were diluted with phosphate-buffered saline to reach a 1:80 suspension, and 10 μ L were incubated with 50 μ L of fluorescein isothiocyanate-conjugated F(ab')₂ goat anti-human IgG (Invitrogen, Carlsbad, CA) for 45 minutes at room temperature. After washing, samples were acquired using a BD FACSLyric flow cytometer, and the data were analyzed using FACSsuite software (both from BD Biosciences, San Jose, CA). Each assay included a positive control (CHECKCELL; Immucor Gamma, Houston, TX) to validate the testing procedure. Results were expressed as median fluorescence intensity.

SARS-CoV-2 RNA viremia was determined in a subset of consecutive patient samples (N = 10) at the Laboratory of Hematology/Oncology, Istituto Europeo di Oncologia. RNA was extracted from 1200 μ L of plasma and 600 μ L of packed cellular fraction using a QIAamp Circulating Nucleic Acid Kit (QIAGEN, Hilden, Germany) and tested by SARS-CoV-2 RNA Droplet Digital PCR System (QX200; Bio-Rad) with Centers for Disease Control and Prevention primers and probes (2019-nCoV Kit;