COVID-19 infection in acute lymphoblastic leukemia over 15 months of the pandemic. A Campus ALL report

The spread of coronavirus disease 2019 (COVID-19), with the two peaks of infection documented worldwide (February 2020-June 2020 and September 2020-April 2021), represented a challenge in the management of patients with hematologic malignancies,[1-3] typically immunosuppressed either because of their primary disease and/or because of treatment. This is particularly true among patients with acute lymphoblastic leukemia (ALL). However, given the rarity of this disease in adulthood, information is limited and based, so far, mainly on case reports,[4-6] with only two larger series having been published.[7,8]

In order to define the clinico-biological features of the COVID-19-infected ALL population, and their ALL management and ALL outcome, as well as COVID-19-related variables, e.g. geographical distribution, source of infection, COVID-19-related support and sequelae, we conducted a cross-sectional, observational study in 34 Italian hematology centers within the nationwide Campus ALL network. The protocol (ref. 2694CESC on 30-04-2020) was approved by the Ethics Committee of the coordinating center and by the local institutional review boards of participating centers. All patients gave written informed consent to participation in the study.

With regard to the geographic distribution of the centers that participated in the study, 17 were located in the north of Italy, 11 in the center and six in southern Italy. The period covered by the survey spanned from February 2020, the start of the first wave of the pandemic, to April 2021, to include the second peak.

Out of 756 adults with ALL (237 with Philadelphia chromosome [Ph]-positive ALL, 363 with Ph-negative B-ALL and 156 with T-ALL) actively followed during this 15-month period, 63 (8.3%, 95% confidence interval [95% CI]: 6.5-10.5) developed an infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), detected by molecular testing in all but one case. No patients had received any anti-SARS-CoV-2 vaccine at the time of the survey. All patients were monitored on a regular basis (in most centers every 3 days) if hospitalized, at hospital admission if outside, whereas for the few patients who were receiving a tyrosine kinase inhibitor (TKI), maintenance and/or were off-therapy (n=6), molecular testing was carried out if they had symptoms or they had a close contact with an infected individual. There was no preferential distribution among the various regions: 30 infections were documented in northern Italy, 19 in central Italy and 14 in southern Italy. Thus, the incidence of the infection in the ALL population in the geographical areas was 7%, 8% and 11.5%, respectively. Most cases were recorded during the second wave of the pandemic. All five COVID-19-positive cases (7.9%) that occurred between February 2020 and April 2020 were recorded in northern Italy, in line with the geographical spread of the first peak of the pandemic. One case (1.6%) was documented between May and August 2020, while 57 cases (90.5%) occurred between September 2020 and April 2021 (Figure 1A-C).

The source of infection was nosocomial in 26 cases (41.3%), familial in 23 (36.5%), unknown in 13 (20.6%) and work-related in one (1.6%).

The features of the 63 infected patients are summarized in Table 1. There was no preferential distribution according to ALL subtype, with COVID-19 occurring in 7.6% of patients with Ph-positive ALL, 7.7% of patients with Ph-negative B-ALL and 10.9% of patients with T-ALL (*P*=n.s.). Of the infected patients, 36 (57.1%) had no comorbidities, 11 (17.5%) had one comorbidity and 16 (25.4%) had more than one comorbid condition (Table 1). COVID-19 infection was documented at the onset of the leukemia and/or during the induction phase in 14 cases (22.2.%), during consolidation in 13, which was TKI-based in two (20.6%), during chemotherapy maintenance in six (9.5%), after allogeneic transplantation in 15 (23.8%), during maintenance with a TKI in seven (11.1%) and off-treatment in six (9.5.%), while in two cases (3.2%) it occurred at relapse.

Of the 63 COVID-19-positive patients with ALL, nine were asymptomatic, ten had only isolated fever, 36 had respiratory symptoms and eight presented other symptoms, including - but not limited to - ageusia and anosmia; notably, the Ph-positive ALL cases were rarely symptomatic (n=3). As a consequence, management of the infection was variable: 29 patients (46%) did not require hospitalization, 28 (44.4%) were hospitalized in a COVID ward and 13 of them required respiratory assistance; finally, six (9.6%) were transferred directly to an intensive care unit (Table 1).

Seven patients succumbed to the infection, with an overall mortality rate of 11.1% (0.9% of the whole cohort); two were male and five were female; three were less than 65 years old. Three out of seven had T- ALL and all were infected at the onset of disease; three had Ph-positive B-ALL, two developed the infection during consolidation and the other at relapse. Finally, among Ph-positive ALL patients, only one death was recorded in an allografted case. In 54 patients (85.7%) there were no sequelae. In one patient pulmonary fibrosis was documented and in another the delay in treatment led to a relapse. In seven cases

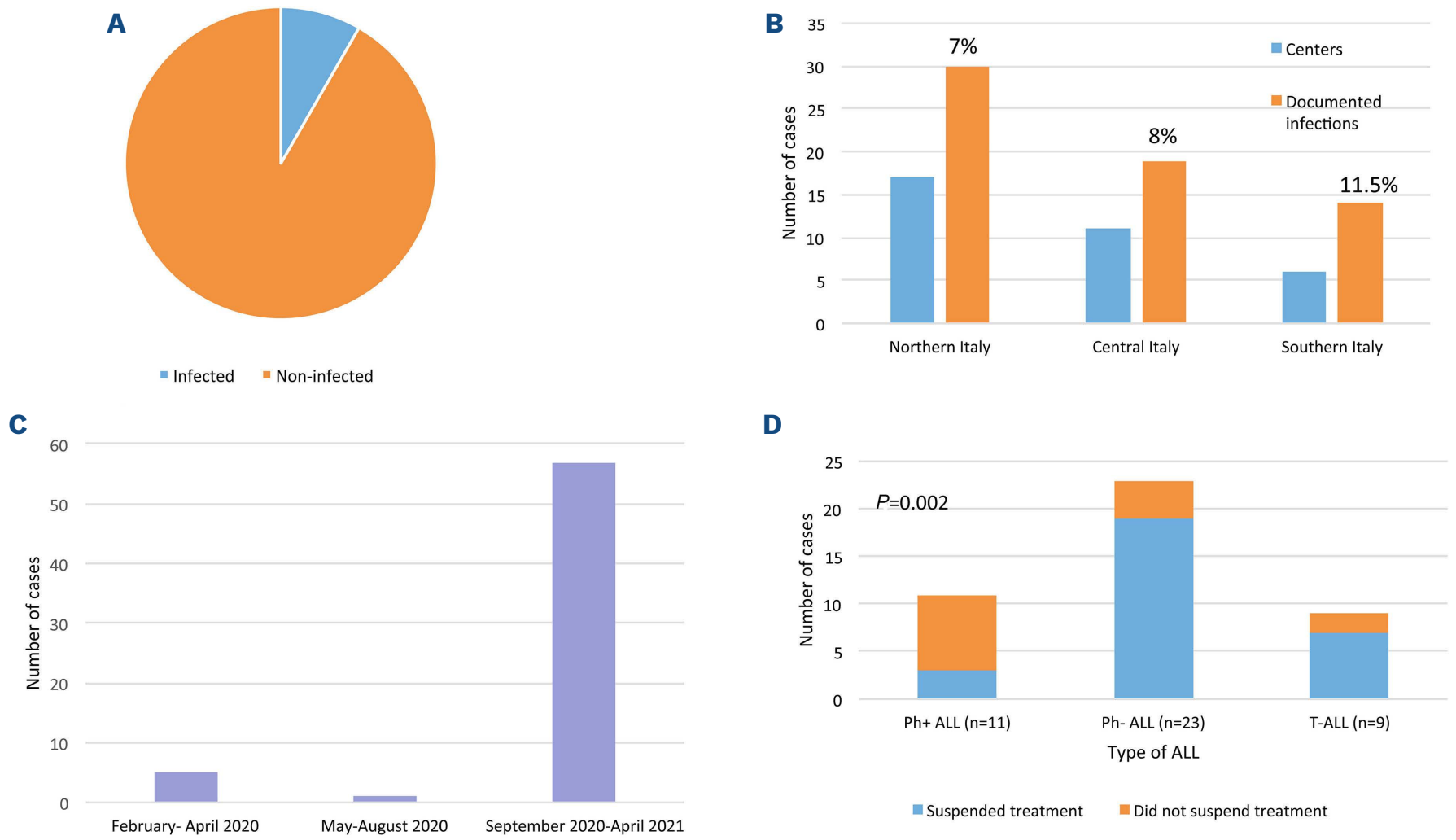

Figure 1. Incidence and distribution of COVID-19, and treatment interruption in patients with acute lymphoblastic leukemia. (A) Percentages of patients with acute lymphoblastic leukemia (ALL) with or without COVID-19. (B) Geographical distribution of infected cases, together with percentages in relation to the geographical area. (C) Distribution of infected cases according to period. (D) Treatment interruption according to the type of ALL.

(9.5%), the infection was still ongoing at the time of the survey and at the latest update (July 2021) it had resolved in all.

Since a key aspect in ALL management is the adherence to the timing of treatment, we also investigated whether COVID-19-positive patients interrupted their ALL treatment during the infection (Figure 1D). Among 43 evaluable patients (patients who underwent hematopoietic cell transplantation - unless receiving therapy for graft-*versus*-host disease - or were off-treatment were excluded), ALL treatment was stopped in 28 (66.6%). Importantly, among 11 Ph-positive ALL patients only three (27.3%) suspended treatment: of these, one was receiving post-transplant treatment (ruxolitinib for graft-*versus*-host disease) and two were on maintenance therapy, whereas of the patients who continued treatment one was in the induction phase with a TKI, two were in consolidation and five were receiving maintenance.

In contrast, among 23 cases of Ph-negative B-ALL, 19 (82.6%) stopped treatment. More in detail, six patients were receiving induction therapy, eight consolidation, two immunotherapy for relapse and three were on maintenance. Of the four patients who continued treatment, one was receiving induction, one consolidation and two were on maintenance. Likewise, also in T-ALL, seven of nine patients (77.8%) stopped treatment: of them, four were in induction, two in consolidation and one in maintenance, whereas the two who continued therapy were in induction. Thus, treatment was interrupted significantly more frequently in T-ALL and in Ph-negative ALL than in Ph-positive ALL (P=0.002), possibly because of the less immunosuppressive treatment received by patients with Ph-positive ALL, and because treatment for Ph-positive ALL does not require hospitalization.

Finally, the median time to obtain viral clearance was 34 days (range, 7-91); this is remarkably longer than the time previously reported in non-hematologic patients, in whom the median time to clearance is 12-14 days, but similar to that reported in other onco-hematologic patients.[9]

Taken together, the results obtained show that the incidence of SARS-CoV-2 infection in ALL patients during 15 months of the pandemic in Italy was similar to that in the general population, and was recorded mostly in the second wave. The largest fraction of infections was nosocomial, despite the use of personal protective equipment by both healthcare personnel and patients, stringent limitation to access for visiting relatives, and constant monitoring of nasopharyngeal swabs. These considerations are particularly important in the light of the new waves of in-

Table 1. Features and in-hospital management of patients with acute lymphoblastic leukemia positive for COVID-19.

Patients (N=63)	
Gender, N (%)	
Male	43 (68)
Female	20 (32)
Age, N (%)	
18-35 years	21 (33)
35-50 years	17 (27)
50-65 years	15 (24)
>65 years	10 (16)
Type of ALL, N (%; % of whole cohort)	
Ph+ B-ALL	18 (28.6; 7.6)
Ph- B-ALL	28 (44.4; 7.7)
T-ALL	17 (27; 10.9)
Comorbidities present; N (%)	
None	36 (57)
One	11 (17)
More than one	16 (25)
Phase of disease, N (%)	
Onset/induction	14 (22.2)
Consolidation	11 (17.4)
Consolidation with TKI	2 (3.2)
Chemotherapy maintenance	6 (9.5)
TKI maintenance	7 (11.1)
Allogeneic SCT	15 (24)
Recurrence	2 (3)
Off-therapy	6 (9)
Most common comorbidity reported, N	
Hypertension	10
Diabetes	2
Obesity	2
Dyslipidemia	1
Metabolic syndrome	1
Parossistic atrial fibrillation	1
Ischemic cardiomyopathy	1
Treatment administered to patients admitted to a COVID ward without need for respiratory assistance (N=15)*, N (%)	
Steroids	8 (53)
Remdesivir	4 (27)
Enoxaparin	4 (27)
Antibiotics	4 (27)
Hydroxychloroquine§	1 (7)
Darunavir/ritonavir§	1 (7)
Treatment administred to patients admitted to COVID ward with need for respiratory assistance (N=13)*, N (%)	
High flow oxygen	8 (61)
Non-invasive ventilation	5 (39)
Antibiotics	8 (61)
Steroids	8 (61)
Enoxaparin	7 (54)
Remdesivir	5 (38)
Convalescent plasma	2 (15)
Hydroxychloroquine§	1 (8)
Lopinavir/ritonavir§	1 (8)
Ruxolitinib	1 (8)
Treatment administred to patientsa dmitted to an Intensive Care Unit (N=6)*, N (%)	
Invasive mechanical ventilation	6 (100)
Antibiotics	4 (67)
Ruxolitinib	1 (17)

*The sum for each category exceeds 100% since patients received more than one type of treatment; §These drugs were used only during the first wave of the pandemic. COVID-19: coronavirus disease 2019; ALL: acute lymphoblastic leukemia; Ph: Philadelphia chromosome; TKI: tyrosine kinase inhibitor; SCT: stem cell transplantation.

fections caused by novel virus variants, and suggest that outpatient and home care should be pursued whenever possible. No enrichment for age, subtype and comorbidities was identified. The infection was manageable, with 46% of patients not requiring any medical intervention. In line with a previous report by our group,[7] it appears that Ph-positive ALL patients were more manageable, requiring fewer treatment interruptions (72.7%). Likewise, in a recent report by the Campus chronic myeloid leukemia (CML) group, the infection and mortality rates in CML in Italy during the pandemic were low, with only 2.5% positive patients (217 COVID-19-positive patients among among 8,665 patients with CML), and a mortality rate of 5.5% and 0.5% in the infected population and entire cohort, respectively.[10] Bonifacio *et al.*[11] reported the serological prevalence of infection in 564 CML patients in different phases of the disease. Eleven patients resulted IgG positive, with only three having a diagnosis of COVID-19. Overall, these observations, although derived from a different setting, suggest a possible protective role of TKI treatment against the severity of COVID-19, as suggested by other studies,[12] although it must be remembered that imatinib does not exert a direct anti COVID-19 effect.[13] Interestingly, also in chronic lymphocytic leukemia, a disorder that occurs predominantly in the elderly and is associated with immune impairment,[14] in which targeted treatment is frequently used front-line (reducing hospital admissions), the incidence of COVID-19 was only 3.3% (494/15,039 cases). These findings support the role of targeted treatment rather than chemotherapy. In this respect, beyond TKI plus monoclonal antibodies in Ph-positive ALL, the use of monoclonal antibodies also in Ph-negative B-ALL is increasing.

Finally, the death rate in our series was 11.1% (<0.9% of the whole cohort), which is better than that recently published by Ribera and colleagues,[8] who reported a mortality rate of 33% in 52 COVID-19-positive ALL patients stratified according to the period of the pandemic (first or second wave). Several reasons might contribute to the lower mortality rate we report. First, in our cohort the majority of patients were infected during the second wave of the pandemic, when the knowledge on the management of COVID-19 was superior. Second, the prevalence of Ph-positive ALL patients was higher in our population (28.6% *vs.* 15% in the study by Ribera *et al.*), as in the elderly population[15], for whom the Italian strategy over the years has been based on TKI-based chemo-free induction without systemic chemotherapy. During the pandemic, the ongoing front-line GIMEMA protocol was based on a chemotherapy-free induction/consolidation with dasatinib and blinatumomab, designed for patients of all ages, with no upper age limit.[16] This approach reduces hospitalization considerably and patients are largely managed as outpatients. Third, our cohort in-

cluded a higher number of patients who contracted the infection during maintenance (20.6% *vs.* 4% in the study by Ribera *et al.*).

Future research will address other crucial issues in ALL patients, such as the efficacy of vaccination and the efficiency and duration of antibody production according to the treatments received and the disease stage, as well as a more thorough investigation of the long-term consequences of the infection.

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No conflicts of interest to disclose.

Contributions

SC, MB and RA analyzed the data, and wrote the manuscript. FG, MA, AC, MIDP, PS, MS, MD, MA, VM, AM, FG, GRC, LS, FL, PC, CP, AMS, MC, MC, MD, FF, CM and MP provided clinical data. FF and GP revised the manuscript. RF planned and designed the survey, analyzed the data, and wrote the manuscript. A complete list of the members of the Campus ALL working group who completed the survey appears in the Appendix.

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Data-sharing statement

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Appendix

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