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LETTER TO THE EDITOR

# Management of chronic lymphocytic leukemia in Italy during a one year of the COVID-19 pandemic and at the start of the vaccination program. A Campus CLL report

## 1 | INTRODUCTION

Twelve months after the outbreak of COVID-19, the Campus CLL network that involves hematology centers throughout Italy completed a survey (Tables 1 and 2) aimed at collecting information on the treatment of chronic lymphocytic leukemia (CLL) patients in the different phases of the pandemic - that is, phase 1 (February–May 2020), phase 2 (June–September 2020) and phase 3 (October 2020–January 2021), as well as on the vaccination program.

During the year of the pandemic, 494 cases of COVID-19 infection were diagnosed among 15.039 CLL cases followed at 47 hematology centers, with a 12-month incidence of 3.3%. This value is comparable with that of the general population in Italy. The majority of CLLs with COVID-19 infection (64%) was observed in the phase 3, with northern regions observing fewer cases than in the phase 1 due to the high incidence observed during the outbreak of the pandemic.[1]

The age of the patients and the type of anti-CLL treatment did not change significantly in the different phases of the pandemic. Because CLL is a disease affecting predominantly the elderly, it comes as no surprise that the median age of CLL patients with COVID-19 infection did not change over time, even though the infection in our country affected the younger population more frequently during the phase 3 (54.6% of the positive cases) than in the phase 1 (28.6%).

The 25% mortality rate did not change significantly in the different phases of the pandemic and appears comparable with that observed previously.[2] We also documented a similar frequency of admissions requiring invasive oxygen support in the high incidence periods, with 21.4% and 20.2% of patients admitted to intensive care units in the phases 1 and 3, respectively.

Our data documented that a higher proportion of patients was followed at home in the summer period (phase 2) compared to those managed during the phase 1 of the pandemic (65% of cases vs. 33.8%, $p = 0.0096$) and also during the phase 3 (39.9% vs. 33.8%, $p$ = ns). These observations suggest that the implementation of outreach services with home care and mobile clinics[3] allowed to release the pressure in hospitals without negatively impacting on survival, especially in the summer period when the low prevalence of the disease enabled an accurate home care follow-up.

## 2 | MANAGEMENT OF CLL THERAPY

Fifty-five percent of centers reported that the pandemic had not impacted significantly on the choice of anti-CLL treatment. Forty-five % of centers felt instead that treatment choices were influenced by the patients' risk of being infected during the travel to the hospital, or by organization issues. Interestingly, the percentage of patients treated with chemo-immunotherapy (CIT) at the time of the COVID-19 infection did not change in the phase 1 (15%) compared to the phase 3 (15.7%), suggesting that this treatment modality maintained its role in a distinct minority of CLL patients. Overall, these findings are likely to reflect the balance between the need of offering the best treatment option to each individual patient and the indication to adopt, as much as possible, treatment regimens that require fewer visits to the clinic.[4,5]

CIT and phosphatidylinositol-3-δ-kinase (PI3KD) inhibitors were withheld at the time of COVID-19 infection. Bruton tyrosine kinase inhibitors (BTKi) and venetoclax were withheld in 53.6% and 66.6% of patients, and the proportion of patients who stopped treatment did not change significantly in the different phases of the pandemic.

The heterogeneous reports by the Campus CLL network on how to treat CLL patients during the reflects the lack of prospective studies. While a prudential treatment hold until recovery has been recommended for patients who develop a COVID-19 infection,[4] no treatment modification for patients with mild symptoms has been recommended in an online forum, where it was also reported that it is common practice to continue BTKis and withhold venetoclax in CLL patients diagnosed with COVID-19.[5] Interestingly, in a prospective study of CIT versus venetoclax-based regimens, 7 patients were diagnosed with COVID-19 and 5 recovered.[6]

## 3 | VACCINATION

In Italy the vaccination policy for patients with hematologic malignancies is heterogeneous, with some hematology centers organizing the vaccination of their patients in the clinic and others

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**TABLE 1** Baseline characteristics, impact on treatment management and outcome of COVID-19 infection in 494 CLL patients by phase of the pandemic in Italy

| Question | No. of patients (%) | | | | |
|---|---|---|---|---|---|
| | Feb 2020–Jan 2021 | Phase 1 (Feb–May 2020) (%) | Phase 2 (Jun–Sep 2020) (%) | Phase 3 (Oct 2020–Jan 2021) (%) | *p* |
| No. of COVID-19+ CLL patients | 494 | 147 (29.7) | 28 (5.7) | 319 (64.6) | |
| Age at COVID-19 infection | | | | | |
| <50 | 26 (5.3) | 3 (2.0) | 0 (0) | 23 (7.2) | 0.075 |
| 50-65 | 144 (29.1) | 48 (32.7) | 12 (42.9) | 84 (26.3) | |
| 65-75 | 171 (34.6) | 47 (32.0) | 10 (35.7) | 114 (35.8) | |
| >75 | 153 (31.0) | 49 (33.3) | 6 (21.4) | 98 (30.7) | |
| Treatment status at COVID-19 infection | | | | | |
| Naïve | 236 (47.8) | 62 (42.2) | 17 (60.7) | 157 (49.2) | |
| Pre-treated | 104 (21.0) | 37 (25.2) | 7 (25.0) | 60 (18.8) | 0.138 |
| On treatment | 154 (31.2) | 48 (32.6) | 4 (14.3) | 102 (32.0) | |
| Ongoing anti-CLL treatment at the time of COVID-19 infection | | | | | |
| CIT | 23 (15.0) | 6 (12.5) | 1 (25.0) | 16 (15.7) | |
| BTKi | 82 (53.2) | 22 (45.8) | 1 (25.0) | 59 (57.8) | 0.155 |
| PI3KD | 8 (5.2) | 4 (8.3) | 0 | 4 (3.9) | |
| V | 27 (17.5) | 14 (29.2) | 1 (25.0) | 12 (11.8) | |
| VR | 14 (9.1) | 2 (4.2) | 1 (25.0) | 11 (10.8) | |
| Anti-CLL treatment withheld because of COVID-19 infection (no. of patients/therapy) | | | | | |
| CIT | 22/23 (95.6)[b] | 6/6 | 1/1 | 15/16 | |
| BTKi | 44/82 (53.6) | 14/22 | 0/1 | 30/59 | |
| PI3KD | 7/8 (87.5) | 4/4 | 0 | 3/4 | 0.395 |
| V | 18/27 (66.6) | 10/14 | 1/1 | 7/12 | |
| VR | 10/14 (71.4) | 2/2 | 1/1 | 7/11 | |
| No. of COVID-19+ CLL[a] | | | | | |
| Followed at home without O2 support | 187 (39.5) | 49 (33.8) | 17 (65.4) | 121 (39.9) | |
| Required non-invasive O2 support | 192 (40.5) | 65 (44.8) | 6 (23.1) | 121 (39.9) | 0.053 |
| Required invasive O2 support | 95 (20.0) | 31 (21.4) | 3 (11.5) | 61 (20.2) | |
| No. of deaths/total no. of COVID-19+ CLL | 122/494 (25) | 44/147 (29.9) | 5/28 (17.9) | 73/319 (22.9) | 0.180 |

Abbreviations: BTKi, Bruton tyrosine kinase inhibitors; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; H, hospital; NA, not applicable; PI3KD, phosphatidylinositol-3-δ-kinase; Tx, treatment; V, venetoclax; VR, venetoclax and rituximab.

[a]Data available in 474 pts.

[b]$p = 0.003$ for the probability to withhold therapy by treatment.

referring patients to dedicated facilities serving a large population. Being aware that vaccination was recommended in patients with hematologic malignancies,[7] we elected to poll the participating centers on their intentions on possible temporary treatment hold before and after vaccination. The majority of centers reported that they planned to advice vaccination to patients undergoing targeted agents without stopping treatment. Nonetheless, 12.2%, 20.5% and 9.5% of centers preferred to withhold BTKis, PI3KD or venetoclax prior to vaccination for at least 1 week and 54.5% of them felt appropriate to offer the vaccination after at least 4 months from the last anti-CD20-containing cycle. Furthermore, 22.7%, 34% and 23% of centers stated that they preferred to hold BTKis, PI3KD or venetoclax treatment for <1 month after vaccination, to ensure a better immunization.

TABLE 2 Vaccination policy in the Campus CLL centers

| Question: would you recommend to withhold anti-CLL treatment before and after vaccination to ensure a better immunization? | | | | |
|---|---|---|---|---|
| Anti CLL treatment | No. of centers that would recommend to withhold therapy before vaccination/ total no. of centers which responded to the question (%) | Length of treatment break before vaccination (months) | % of centers that would recommend to withhold therapy after vaccination | Months between vaccination and restart of treatment |
| CIT | 13/44 (29.5) | 1–2 | NA | NA |
| | 11/44 (25.0) | 3–4 | | |
| | 20/44 (45.5) | >4 | | |
| BTKi | 36/41 (87.8) | No break | 22.7 | <1m |
| | 3/41 (7.3) | <1 | | |
| | 2/41 (4.9) | >1 | | |
| PI3KD | 31/39 (79.5) | No break | 34 | <1m |
| | 5/39 (12.8) | <1 | | |
| | 3/39 (7.7) | >1 | | |
| V | 38/42 (90.5) | No break | 23 | <1m |
| | 3/42 (7.1) | <1 | | |
| | 1/41 (2.4) | >1 | | |

Abbreviations: BTKi, Bruton tyrosine kinase inhibitors; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; NA, not applicable; PI3KD, phosphatidylinositol-3-δ-kinase; V, venetoclax; VR, venetoclax and rituximab.

## 4 | CONCLUSIONS

The results of this 12-months analysis documented the overall low incidence of COVID-19 infection in CLL patients (3.3%), similar to that of the normal population in Italy. Patients 'age and severity of the disease did not vary significantly in the two high-incidence phases, confirming that CLL patients with COVID-19 are at a relatively high risk of intensive oxygen support despite improvement in the diagnostic tracing and definition of anti-COVID-19 treatment protocols.[8]

Remarkablly, 55% of centers did not report a significant impact of the pandemic on treatment choices, a finding that reflects an efficient organization effort allowing a safe access of patients to the outpatient department. The policy of withholding anti-CLL treatment did not change significantly in the different phases of the pandemic possibly due to the adoption of guidelines shared by treating physicians at each center.[4]

Lastly, the differences in the recommendations on possible anti-CLL treatment holds before and after COVID 19 vaccination reported in this survey reflect uncertainties in the scientific community pointing to the need of evidence-based recommendations, especially in view of recent published data showing that CLL patients under treatment have a low likelihood of mounting an immune response after vaccination.[9,10]

KEYWORDS
chronic lymphocytic leukemia, COVID-19, targeted agents, vaccination

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## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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## TRANSPARENT PEER REVIEW

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