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# CHRONIC LYMPHOCYTIC LEUKEMIA MANAGEMENT IN ITALY DURING THE COVID-19 PANDEMIC. A CAMPUS CLL REPORT

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**Abstract:**

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**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 the health authorities issued rules to: i) determine which patients and health personnel should be tested by nasopharyngeal swab for Covid-19 infection, ii) limit access to the hospitals for outpatient visits which could be postponed, and iii) regulate the access of personnel to laboratory activities. To analyze the impact of these recommendations on the management of chronic lymphocytic leukemia (CLL) - 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 addressing three different issues: i) strategy for testing by nasopharyngeal swab; ii) impact of the Covid-19 outbreak in the diagnosis, management and outcome of CLL patients; iii) 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 on the entire territory and are following on a regular basis at least 100 CLL patients per center (range 100-700, median 200). Eighteen centers were based in Northern Italy (North of Rome), mostly affected by the Covid-19 outbreak. This survey is based on 9930 CLL patients managed during the Covid-19 pandemic, accounting for approximately one third of all CLL patients in Italy. The results are shown in Table 1 and allow some considerations.

*Strategies for testing for Covid-19+ cases*

Testing strategies for Covid-19 infection were not homogeneous throughout the country. The minimal by-law 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 prior to treatment only in 30.3% of centers, a strategy that reflects the higher capacity of some regional health systems to perform and analyze nasopharyngeal swabs.

Overall, 47 symptomatic patients were found to be Covid-19+ as of April 15 in our cohort of 9330 CLL patients followed at the 33 centers (0.5%). The large majority of Covid-19+ patients came from the four regions more heavily affected by the pandemic: Lombardia, Piemonte, Veneto, Emilia-Romagna. The centers involved in this survey are managing CLL patients on a regular basis and although some Covid-19+ cases may have been missed, the 0.5% prevalence recorded is likely to represent 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 telephone interviews to all CLL patients and no additional symptomatic cases were detected.



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The prevalence of Covid-19 positivity in 60.36 million inhabitants in Italy as of April 15 was 0.27% (data available at https://lab24.ilsole24ore.com/coronavirus/?utm_source=fasciahp#box_1), independently of age. It is worth noting that unlike our CLL patients, many symptomatic individuals without coexisting conditions have so far not been routinely tested in our county. These findings indicate that the overall prevalence of symptomatic Covid-19+ CLL is low and not significantly higher than that of the normal population despite the advanced median age of CLL patients, the known associated immunosuppression and the possible impact of treatment. This observation is in line with what recorded also in Ph+ acute lymphoblastic leukemia (Ph+ ALL) (1) where the incidence increases with age, as well as in chronic myeloid leukemia (CML) (2,3) where the median age is around 60 years.

*Diagnosis and management of CLL patients*

With few exceptions (3/33 centers) a triage is set up in order to identify symptomatic patients who are then tested in a dedicated area and the spaces are large enough to allow for an adequate social distancing (i.e. >1 meter) virtually in 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 work-up and prognostic stratification of patients, a process of utmost importance for a correct management of CLL (4,5), in 15.2% of centers.

Our survey shows that the Covid-19 outbreak has impacted on treatment. It was in fact observed that: i) treatment initiation was carried out without delay in only 21% of centers; ii) administration of ongoing treatment was delayed in 24% of centers and in 1 center rituximab was suspended; iii) 45.5% of centers were advised to reduce usage of blood product as much as possible due to shortage of donors and in two instances donors were found to be Covid-19+ with no known impact on the patients; and iv) planned post-treatment restaging had to be postponed in 30.3% of the centers.

With regard to 46 Covid-19+ patients for whom we were able to collect clinical information, the infection occurred in both treated and untreated patients. More in detail, 16 CLL patients had never been treated, 15 were on front-line or salvage treatment (5 on ibrutinib, 4 under chemoimmunotherapy, 6 undergoing other treatments), 9 were within six months of stopping chemo-immunotherapy and 6 had been treated earlier. Fourteen patients never required



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oxygen/ventilation, while 32 patients did. As of May 18, 28 patients have fully recovered, 4 are in hospital, 2 with non-invasive oxygen support, and 14 have died, with a morality rate of 30.4% (median age 75, range 51-91). As of the same date (May 18), the mortality rate for symptomatic Covid-19 patients amongst the general population in Italy was 13.4%, and 25.5% in the 70-79 year-old population (https://www.epicentro.iss.it/coronavirus/).

In a recent online paper in Blood (6), it has been hypothesized that the BTK inhibitor ibrutinib may play a protective role against pulmonary injury in Covid-19 infected Waldenstrom's macroglobulinemia (WM) patients. The authors were asking for further validation in other patient populations on ibrutinib treatment, namely CLL. So, far we could not associate the clinical course, aggressiveness, outcome to the type of treatment, if any.

*Enrolment and adherence to clinical protocols*

We finally investigated the level of enrolment 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 and follow-up of patients on protocol. Contrariwise, CROs stopped or slowed accrual in 33% of centers, while there were no new enrolments due to the hematologist's decision or patient refusal in 17% of centers and problems with follow-up visits of enrolled patients in 17% of centers.

*Conclusions*

Our survey on the management of CLL during the current pandemic allows some broader considerations. CLL patients appear to have been so far scarcely affected by Covid-19 during the outbreak and peak of the infection in Italy, irrespective of the median age of patients, the associated immunosuppression and treatment. Even through the Covid-19 pandemic patients have largely continued to be adequately managed. The numbers are too small to define if the mortality in Covid-19+ CLL patients is higher than that of the normal population matched per age and if BTK inhibitors may have a protective effect.

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



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enrolled in clinical trials and on the monitoring of such patients. All the above will represent an objective limit if the pandemic will not ease out rapidly.

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

| **QUESTIONS** | **N. 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+ subjects | |
| - No | 23 (70%) |
| - Yes | 7 (21%) |
| - Yes, at least twice | 3 (9%) |
| CLL patients are tested by nasopharyngeal swab | |
| a) Only if presenting with with flu-like illness and/or close contact with a Covid-19+ subject | 23 (70%) |
| b) As in a) 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 distance (i.e. >1 meter) 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 days a reduction of newly diagnosed CLL patients | |
| - Yes | 20 (61%) |
| - No | 13 (39%) |
| Did you face problems in the diagnostic work-up | |
| - Yes | 5 (15%) |
| - No | 28 (85%) |
| PhD students and post-doctoral fellows involved in work-up of CLL patients | |
| - 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 Covid-19+ CLL patients managed | |
| - Followed 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%) |

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| | |
|---|---|
| | |
| 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 post-therapy | |
| - Were visited without delay | 23 (70%) |
| - Were rescheduled >1 month later | 10 (30%) |
| The usage of blood or platelet transfusion | |
| - Had no restriction | 16 (48.5%) |
| - Had no restriction with an alert that donors were found to be COVID-19+ (not transmitted to the patient) | 2 (6%) |
| - We were advised to reduce usage of blood product as much as possible due to shortage of donors | 15 (45.5%) |
| | |
| **Clinical trials** | |
| Enrollment of CLL patients 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%) |

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