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Scientific Letter

Venetoclax-Rituximab Treatment of Relapsed/Refractory CLL During the COVID-19 Pandemic: A Real-Life Experience in Selected Central-Southern Italian Regions

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To the editor.

With more than 3 million proven infections and 100.000 associated deaths in Italy, the COVID-19 pandemic poses extraordinary challenges to healthcare professionals and especially to those caring for patients with hematologic malignancies.[1-2] Furthermore, given the multiple immune defects characterizing chronic lymphocytic leukemia (CLL), it is considered that patients with this form of leukemia have a high risk of suffering severe forms of COVID-19.[3-4]

Several studies have reported on the correlation between CLL and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, but most of them are from the first wave of the outbreak and consist of editorials, letters to the editor, commentaries, and conference proceedings.[5-12] Only two multicenter cross-sectional studies have included a large number of patients with CLL and symptomatic COVID-19(13-14). These studies enrolled 190 and 198 patients with CLL and symptomatic COVID-19, respectively. The majority of patients were on Bruton Kinase inhibitor (BTKi) therapy at the time of COVID19 infection (61 and 44 cases, respectively), while only a small group of patients were treated with venetoclax-based regimens (9 and 17 cases, respectively).[13-14]

In order to guide clinicians treating CLL patients, USA and European hematological organizations (American Society Hematology [ASH], European Hematological Association [EHA]/European Research Initiative [ERIC] on CLL) have released a series of recommendations for proper management of CLL patients during the COVID19 outbreak.[15-16] Among other counsels, it is suggested: "to avoid or skip treatment with monoclonal antibodies (i.e., rituximab, obinutuzumab) especially when given in combination with targeted agents." Also, "treatment with venetoclax, which requires frequent clinic visits with lab assessment, should be avoided if possible unless considered the most appropriate treatment for a particular patient".[16-17] However, how these recommendations affect CLL patients' care in the real world has not been assessed.

An exploratory survey was undertaken in selected regions of central-southern Italy (i.e., Umbria, Campania, Puglia, Calabria, and Sicilia) to ascertain the adherence to the recommendations mentioned above. That study also aimed to assess the prevalence and severity of COVID19 infection among CLL patients homogeneously treated in an area with an estimated population of about 18 million inhabitants. The target population consisted of patients with relapsed/refractory (R/R) CLL treated from February 1th to Dec 31th 2020 with time-limited venetoclax/rituximab (VR) combination as employed in the MURANO trial (i.e., venetoclax for up to 2 years plus rituximab for the first 6 months). The data collecting form focused on whether a test for detection of COVID-19 infection was performed only in patients with CLL who reported symptoms or universally; detailed information of the cases who contracted COVID-19 infection, its severity and outcome; and treatment modifications once the infection was detected.

The questionnaire was sent to 30 CLL hematologists, of which 26 responded. Finally, we considered suitable for the present analysis the 24 questionnaires compiled by hematologists who declared to have treated at least one patient with VR combination in the observation period. Of those, 20.8% worked in academic hospitals.

Overall, the survey allowed data collection on 124 patients who had begun treatment with VR combination for R/R CLL no earlier than February 1st, 2020. The median number of patients treated in each center was 5 (range, 1-15).

COVID-19 surveillance tests consisted of viral RNA reverse transcriptase PCR (RT-PCR) on nasopharyngeal swabs. Most patients (83/124, 66.9%) were tested before beginning the ramp-up with venetoclax; moreover, 66/124 (53.2%) were regularly tested before each rituximab infusion.

The treatment adherence was relatively high (70.8%). Only 20.8% of physicians modified the therapeutic program, mainly because of WHO grade 3 neutropenia. Changes consisted of transient interruption of venetoclax (22%), reduction of doses (48%), and delay of rituximab infusion (30%). Only 2 (8.3%) physicians declared to have skipped or delayed rituximab infusions due to the concern about the potential higher risk of infection associated with anti-CD20 monoclonal antibodies combined to targeted agents.

Overall, 2/124 patients (1.6%; 95% confidence interval [CI], 1.2-9.5%) had symptomatic RT-PCR proven diagnosis of COVID-19 infection and required hospitalization. Both patients needed oxygen therapy and admission into an intensive care unit. Of those, one patient who was receiving VR combination at the time of COVID infection eventually died. The second patient developed COVID-19 infection while receiving venetoclax monotherapy (after the VR combination period). He recovered from a COVID-19 infection, and after 21 days of treatment interruption, he was able to restart venetoclax. Despite the relatively close surveillance policy (i.e., approximately 70% of patients had a molecular nasopharyngeal swab at the start of venetoclax ramp-up and 53.2% before each rituximab infusion), no case of asymptomatic or paucisymptomatic COVID-19 infection was observed.

The current study assessing the frequency and severity of COVID19 infection in a homogeneous cohort of patients with R/R CLL treated with VR is worth being compared with other reports. Compared to the Italian CLL Campus data, which includes a patient population heterogeneous for treatment, our findings indicate only an apparent higher incidence of COVID19 infections (i.e., 0.5% versus 1.6%). It is worth noting that our study examined the entire COVID19 outbreak period, whereas the CLL Campus analysis only looked at the first two months, resulting in a likely underestimation of the COVID19 infection rate.

The current study also provides information on the strategy used to monitor CLL patients who were suitable for a therapeutic approach that requires, at least initially, regular clinic visits, which may theoretically conflict with a primary prevention policy. For example, in a survey conducted in the USA at the beginning of the outbreak, only 23% of clinicians recommended universal testing for all patients.[5] In our survey, 66.9% and 53.2% of patients were tested with molecular swabs, respectively, at the beginning of venetoclax and later before each rituximab infusion. Following these measures, physicians were confident in the use of the VR combination and provided patients unconditional continuation of CLL therapy unless a treatment-related adverse effect occurred (i.e., mainly WHO grade 3 neutropenia).

To summarize, the findings of this study provide previously unknown details about the use of VR combination therapy in CLL patients in real-world clinical practice during the COVID19 pandemic. Our understanding of the COVID-19 pandemic is constantly evolving, and so are recommendations and practices. While waiting for results of ongoing observational and interventional studies to inform evidence-based recommendations, our survey suggests that VR time-limited combination therapy can be used safely in the era of the COVID19 outbreak. Moreover, recent access to vaccines against SARS-CoV-2 offers a unique chance to answer important practical questions.[17] Since the quality of a serologic response is scarce in CLL, the clinical impact of vaccination on the risk reduction for SARS-CoV-2 infection is a matter of study.[18] We also need to know whether differences in seroconversion in patients receiving small molecules (BTKi, BCL2i) *vs.* venetoclax exist.

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