Mild Clinical Course of COVID-19 Infection in Chronic Myeloid Leukemia (CML) Patients Receiving Tyrosine Kinase Inhibitors (TKIs) without Interruption

Keywords: CML; SARS-CoV-2; COVID-19; TKI; ABL; 25-OH vitamin D.

To the editor.

In Hungary, the first two SARS-CoV-2 cases were diagnosed on March 4, 2020.1 During the first wave of the pandemic, a large proportion of reported cases occurred in institutions, mainly in nursing homes. Thus tremendous efforts were made to screen, especially those living in nursing homes.

The first of the three CML patients we report is a 88 years old female patient living at a nursing home and receiving imatinib treatment because of chronic myeloid leukemia (CML) for 7 years. Her nasal swab was found to be COVID-19 PCR positive in the course of routine screening in April 2020. Another COVID-19 PCR was positive two weeks later again, though no other signs or clinical symptoms were found aside from profound weakness. Imatinib treatment was continued unchanged during COVID-19 infection. Since then, two further CML patients treated at our hematological center were found to have acquired COVID-19 infection. The main clinical characteristics of these three patients are summarized in Table 1.

The second patient, a barber, tested PCR positive for Covid-19 five days after the first symptoms, he had no symptoms 10 days later anymore, but his PCR was still positive and was negative 15 days after the first test, allowing him to return to work. The third patient might have acquired Covid-19 from his companion, a nurse who suffered Covid-19-infection. At the diagnosis of CML in 2010, this patient was treated with imatinib first line, was switched later to nilotinib second line and dasatinib third line without achieving major molecular response (no mutation was identified). Thus we started treatment with 500 mg bosutinib/day in March 2015.

Table 1. Main clinical characteristics, treatment and disease course of three patients with CML and COVID-19 infection.

<table>
<thead>
<tr>
<th>#</th>
<th>gender</th>
<th>age</th>
<th>co-morbidities</th>
<th>COVID symptoms</th>
<th>COVID category</th>
<th>COVID treatment</th>
<th>CML dg. calendar year and prognostic score</th>
<th>TKI</th>
<th>Molecular remission status at COVID</th>
<th>COVID outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>88</td>
<td>hypertension, generalized arteriosclerosis</td>
<td>weakness</td>
<td>mild</td>
<td>none</td>
<td>2013 Sokal score 1,01 (intermediate) ELTS score 2,638 (high risk)</td>
<td>imatinib</td>
<td>MR5</td>
<td>recovered</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>43</td>
<td>none</td>
<td>weakness, sore throat, fever</td>
<td>mild</td>
<td>amoxicillin + clavulanic acid</td>
<td>2006 Sokal score 0,64 (low) ELTS 2,0525 (intermediate risk)</td>
<td>imatinib</td>
<td>MR4</td>
<td>recovered</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>47</td>
<td>NSTEMI subtotal CX occlusion, PCI in 2015</td>
<td>coughing, fever, diarrhoea, anosmia</td>
<td>mild</td>
<td>azithromycin</td>
<td>2010 Sokal score 0,66 (low risk) ELTS 3,9847 (high risk)</td>
<td>bosutinib (fourth line)</td>
<td>MR4</td>
<td>recovered</td>
</tr>
</tbody>
</table>

* COVID-19 IgG antibodies (using an Abbott SARS-CoV-2-Ig test) were found to be present in our patients 6 month, 10 weeks and 5 weeks following the COVID-19 infection, respectively. As vitamin D has been suggested to be an additional factor in improving outcomes in patients with COVID 19 infections, we also tested for 25-OH vitamin D serum levels at these time points. Serum 25-OH vitamin D levels were found to be normal in all the three patients (44.6 ng/ml, 33.5 ng /ml and 48.1 ng/ml, respectively (normal values: 30-60 ng/ml)). ** NSTEMI: non-ST-elevation myocardial infarction. PCI: percutaneous coronary intervention. CX: circumflex artery. ELTS: EUTOS (EUropean Treatment Outcome Study) long-term survival score.
without side effects, and the patient got into deep molecular response (DMR). In November 2015, anjinal symptoms developed with elevated cardiac biomarkers of necrosis in the absence of persistent ST-segment elevation (NSTEMI), a coronarography proved subtotal circumflex artery (CX) occlusion, a percutaneous coronary intervention (PCI) was performed. His cardiological follow-up is uneventful; he performs moderate sport activities and is in continuous DMR. Two weeks after his positive COVID-19 PCR test, he was symptom-free, his Covid PCR was still positive (it became negative further two weeks later).

Though coronavirus disease 2019 (COVID-19) pandemic poses several challenges to managing patients with leukemia, CML patients treated with TKIs seem to represent a unique patient population in this respect. In May 2020, Abruzzese et al. reported the relatively mild clinical course of COVID-19 infection in a patient who continued full-dose dasatinib therapy when diagnosed with COVID-19. The authors suggested that the incidence and severity of SARS-CoV-2 virus infection may not be worse in CML patients treated with TKIs than in virus victims without an underlying CML diagnosis and that CML patients who contract SARS-CoV-2 may even be protected by TKI therapy. A previous in vitro research - aimed at repurposing approved drugs for the treatment of emerging coronaviruses - has shown that imatinib's anti-coronavirus activity occurs at the early stages of infection, after internalization and endosomal trafficking, by inhibiting fusion of the virions at the endosomal membrane. The authors specifically identified the imatinib target, Abelson tyrosine-protein kinase 2 (Abl2), as required for efficient SARS-CoV (and MERS-CoV replication) in vitro. Ongoing studies intend to evaluate the efficacy and safety of oral administration of imatinib in hospitalized patients with COVID-19 (ClinicalTrials.gov Identifier: NCT04394416) and the potential of oral imatinib to prevent pulmonary vascular leak in COVID-19 patients.

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Competing interests: The authors declare no conflict of Interest.

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