


# Is COVID-19 less severe in CML patients than in those with other haematological cancers?

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Commentary on: Breccia M *et al.* COVID-19 infection in chronic myeloid leukaemia after one year of the pandemic in Italy. A Campus CML report. *Br J Haematol*, 2022;196:559–565.

COVID-19 has been a difficult challenge for the healthcare system, being responsible for more than 4.5 million deaths worldwide to date.

In addition to age and cardiovascular, respiratory and metabolic comorbidities, cancer has been found to be associated with worse COVID-19 outcomes.<sup>1</sup> This also applies to haematological malignancies, and some authors have even demonstrated that these patients are at increased risk of death during COVID-19-associated hospital admission compared with patients suffering from solid cancers.<sup>2</sup>

Several reports highlighted the more severe COVID-19 manifestations in patients with myeloid neoplasm,<sup>3</sup> lymphoma,<sup>4</sup> myeloma<sup>5</sup> and chronic lymphocytic leukaemia,<sup>6</sup> with a mortality rate exceeding 30% in some studies.<sup>7,8</sup> It is not yet clear whether the aggravating factor in such cases derives from the disease itself and its complications or from the immunosuppressive effect of treatments (chemotherapy, stem cell transplantation, proteasome inhibitors, monoclonal antibodies, molecular target therapies), but it is reasonable to think that it originates from the combination of the two players. A recent study showed that haematological and solid cancers negatively affect the COVID-19 course also in the paediatric population,<sup>9</sup> suggesting that the effect is independent from age. Consequently, onco-haematological patients have been included in the highly vulnerable group in several countries during the pandemic, and, as such, they have benefited from shielding measures and have been prioritised in vaccination campaigns.

At the moment, we still lack enough evidence to understand whether the risk of more severe COVID-19 forms differs across the several types of haematological neoplasms.<sup>10</sup>

Initial, very limited data pointed towards an overall mild COVID-19 course in patients with chronic myeloid leukaemia (CML), comparable to that reported in the general population.<sup>11</sup>

The work from Breccia *et al.*<sup>12</sup> is very relevant in this regard, as it is the largest study describing the outcome of COVID-19 in CML patients. The authors (members of the Campus CML working group) conducted a nationwide survey across more than 50 Italian centres. They collected clinical data on the incidence, the severity and the outcome of PCR-confirmed SARS-CoV-2 infection during the first year of the pandemic in Italy and also analysed the impact of COVID-19 on the management of these patients. Out of 8,665 CML patients, 217 got the infection. Importantly, COVID-19 severity was overall comparable to that seen in the general population: most CML patients were asymptomatic or suffered from the mild form of the disease, and up to 170 patients did not require hospital admission and were only quarantined. Twelve patients died, with a mortality rate of 5.5%, which was lower compared to that found in the available literature on other haematological malignancies, but still slightly higher than in the Italian population (2.97%). Interestingly, results from the Italian study are more encouraging than those reported by the global CANDID study,<sup>13</sup> in which a mortality rate of 13.7% was observed in 110 CML patients diagnosed with COVID-19 up to early July 2020.

Breccia *et al.* found that older age, cough as presenting symptom, imatinib therapy and presence of cardiovascular comorbidities were significantly associated with COVID-19-related mortality in univariate analysis.

The relatively large number of patients in this study offers a more solid ground to the conclusion of a lighter COVID-19 in CML patients compared to other blood cancers.

As explanation of their findings, Breccia and co-workers postulated that, apart from the relatively lower morbidity associated with CML and its treatment as opposed to other haematological cancers, a potential mitigating effect exerted by BCR-ABL1 tyrosine kinase inhibitors (TKI) on the course of COVID-19 cannot be ruled out. This would occur through a possible anti-viral action of TKI, as previously described against other viruses. About this aspect, a structure-based computational screening approach has recently identified nilotinib among drugs with the potential of binding SARS-CoV-2 targets and affecting its replication.<sup>14</sup>

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It is important to note that in this Campus CML working group's study, which reflects the common 'real-life' composition of CML cohorts in developed countries, most of the subjects (85%) were in major or deep molecular responses. In this regard, although TKI have been described as potentially immunosuppressive,<sup>15</sup> it has recently been shown that CML patients on TKI move from the immunosuppression associated with full-blown disease<sup>16</sup> to the restoration of immune function at the achievement of deep molecular response.<sup>17</sup> Furthermore, in favour of a functional immune system in CML patients on TKI is the observation that they are able to mount both humoral and cellular responses to anti-SARS-CoV-2 vaccine,<sup>18</sup> which is not the case for other haematological malignancies.<sup>19,20</sup> In addition, single-centre<sup>21</sup> and multicentre<sup>22</sup> studies demonstrated that prevalence of anti-SARS-CoV-2 antibodies during the first wave of pandemic in CML patients was similar to that observed in the general population, suggesting a similar susceptibility to the infection in the two groups.

Altogether, the above evidence is in line with a relatively limited morbidity and mortality of COVID-19 in CML patients. However, caution should always be used before drawing definite conclusions. Very large prospective studies are needed to truly ascertain the COVID-19 course in each group of onco-haematological patients, as they would allow proper adjustment for important factors like age, disease status (active disease, partial or complete response), ongoing therapies and context (*i.e.*, socioeconomic milieu and country of origin, hospitalised versus non-hospitalised patients). In this regard, the updated results of the global CANDID study in CML patients will be of great value for the scientific community.

Finally, although the data from this Italian work are reassuring for patients and their clinicians, considering CML patients at high risk of COVID-19 fatality is still a very reasonable and prudent approach and should be used to tailor infection-preventive strategies and treatment pathways accordingly, at least until more robust data become available.

## Conflict of interest

None.

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