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EDITORIAL

Chronic myeloid leukaemia and the use of tyrosine kinase inhibitors in the days of COVID-19 pandemic

Tyrosine kinase inhibitors (TKIs) have revolutionized the management of chronic myeloid leukaemia (CML). Currently in patients with CML in chronic phase (CML-CP), breakpoint cluster region-Abelson (*BCR-ABL*) targeted TKIs are the first-line treatment modality used in almost all cases.[1]

Many countries are experiencing an outbreak of a novel betacoronavirus known as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).[2,3] The World Health Organization has declared 2019 novel coronavirus disease (COVID-19), caused by SARS-CoV-2, a public health emergency of international concern, since it is characterized by rapid human-to-human transmission.[3]

The median age of patients with CML at diagnosis is approximately 50–60 years in most of the registries, and patients with malignancy are usually characterized by older ages, multiple complicated diseases, which are also true for cases with CML. Although advanced phase disease (accelerated phase and blast crisis)[4] can be associated with immune suppression and a high risk for infections, neither CML-CP nor *BCR-ABL* TKIs induce clinically significant immune suppression. Knowing the fact that older age, significant comorbidities, and lower immunity may lead to a higher probability of severe illness and increased mortality compared with the healthy population once infected with COVID-19,[3] to date, there are no data suggesting that patients with CML-CP are at higher risk of infection by SARS-CoV-2 than the general healthy population.

This paper mainly focuses on CML treatment in COVID-19 pandemic, where TKI therapy can be hard to manage together with the medications used in the management of SARS-CoV-2 infection due to potential drug-drug interactions.

Although generally well tolerated, all *BCR-ABL* TKIs can be associated with haematologic and non-haematologic toxicities,[5,6] and most of the patients with CML-CP continue receiving TKIs, unless there is lack of optimal response and/or serious toxicities. TKI-associated haematologic toxicities (myelosuppression) are both due to the suppression of the leukaemic clone and the inhibition of non-leukaemic haematopoiesis.[7] Myelosuppression is usually limited to the first weeks or months of TKI therapy, and the incidence of grade III-IV myelosuppression is usually predominant only at the initial phase of the TKI treatment, decreasing substantially with longer duration of any TKI therapy.[7] If severe cytopenias occur, this may hypothetically increase the risk of severe COVID-19. In addition to that, TKI-induced pulmonary diseases[8–10] may result in dismal outcomes of the COVID-19. Having said that, CML-CP patients do not appear at a higher risk of getting COVID-19, although data are still limited. In one multicentre study coming from China, consisting of 392 CML patients, there were 4 patients with definite contact with COVID-19, and 12 cases had fever, cough, or shortness of breath during the epidemic.[11] One patient had confirmed COVID-19 and cured after treatment. Some preclinical data showed that imatinib and nilotinib may have therapeutic efficacy in the management of some viral diseases,[12] and future research in the field of SARS-CoV-2 evaluating the efficacy of TKIs might be of interest.

Chloroquine/hydroxychloroquine and azithromycin were thought to be beneficial in the management SARS-CoV-2 infection, although these drugs are not yet proven to be curative in patients with COVID-19. Since TKIs are generally used as a long-term treatment and they are metabolized by cytochrome-P450 (CYP) enzymes, patients receiving these drugs are at substantial risk of having drug-drug interactions.[13–15] Furthermore, because of the oral administration route of TKIs, drug-drug interactions concerning gastrointestinal absorption have become apparent as well. So, for my point of view, the main concern about the CML patients on TKI therapy, who have COVID-19, is the potentially drug-drug interactions between the TKIs and the drugs used in the treatment of COVID-19 (especially chloroquine/hydroxychloroquine and azithromycin).

The most commonly used TKI in newly diagnosed CML patients is imatinib, and chloroquine may increase imatinib exposure due to inhibition of P-glycoprotein and it may also cause decreased intracellular exposure of imatinib because of hOCT1 inhibition.[16] Similarly, chloroquine use may result in increased exposure of dasatinib due to P-glycoprotein inhibition.[16] No such interaction was demonstrated between TKIs and azithromycin.[16] So, checking for the plasma levels of TKIs (e.g., imatinib) has clinical value in terms of both efficacy and toxicity. In addition to that, CYP2D6 is involved in the metabolisms of both chloroquine and hydroxychloroquine.[17,18] They may also inhibit the activity of CYP2D6,[19] which potentially has an impact on the plasma levels of other drugs that are metabolized by CYP2D6 such as imatinib. Imatinib is a competitive inhibitor of CYP2D6,[19] thus may result in elevated plasma levels of chloroquine/hydroxychloroquine, when these drugs are co-administered.[20]

In a recent study, where the authors randomly assigned 62 patients with CML-CP into two groups as one group consisting of cases continuing imatinib alone (n = 30) and the other group containing cases who received imatinib in combination with hydroxychloroquine (n = 32), it was shown that at 12 and 24 months, major molecular response rates were higher in the combination arm than those of the imatinib arm, although the differences were not

significant.[21,22] The standard dose for hydroxychloroquine therapy in this study was 400 mg twice daily (800 mg/day totally)—twice the dose recommended to be used in COVID-19. There were no differences regarding plasma trough imatinib levels between the combination and the imatinib alone arms, whereas the plasma levels of imatinib metabolite were significantly higher in the combination arm than the imatinib arm.[21]

All TKIs used in the treatment of CML and have the capacity to prolong the QTc interval that can lead to torsades de pointes and sudden death.[23] Prior to starting TKI therapy, an initial electrocardiogram (ECG) should be performed,[24] and in general, the normal QTc interval is 400 to 440 ms. Similarly, chloroquine[25] and azithromycin[26] can also cause QTc prolongation, so close monitoring of QTc interval with serial ECG analysis together with measurement of electrolytes are crucial in patients with CML receiving TKIs and especially chloroquine/hydroxychloroquine plus azithromycin due to COVID-19.[16] In the study by Horne et al.[21] patients with a screening ECG with a QTc > 450 ms, congenital long QT syndrome, history or presence of sustained ventricular tachycardia, and any history of ventricular fibrillation or torsades de pointes were excluded from the study.

Favipiravir is an antiviral medication, which was used in the Ebola virus disease pandemic, is a promising agent in the treatment of SARS-CoV-2 infection.[27] This drug was also shown to associated with QTc prolongation,[28] so extra caution is also required in a CML patient on TKI treatment, when favipiravir is needed to be initiated due to COVID-19.

According to common terminology criteria for adverse events (CTCAE) v5.0, QTc prolongation is graded as grade I: QTc 450–480 ms, grade II: QTc 481–500 ms, grade III: QTc ≥ 501 ms or 60 ms change from baseline, and grade 4: torsade de pointes, polymorphic ventricular tachycardia, and signs/symptoms of serious arrhythmia.[29] In the case of QTc > 440 ms or prolongation of >30 ms from baseline, strict ECG monitoring (at least weekly) is recommended. In the case of QTc >500 ms (grade III) or prolongation of >50 ms from baseline, temporary TKI cessation is recommended, followed by weekly ECG and TKI resumption when QTc ≤ 450 ms in two consecutive ECGs.[24] In patients receiving nilotinib, resumption at a lower dose is recommended once the QTc falls in this way, without subsequent re-escalation.[14]

The SARS-CoV-2 emerged in December 2019 and then spread rapidly worldwide, and COVID-19 can be severe, which can be especially problematic in patients with both solid and haematologic cancers.[30] To date, patients with CML-CP on TKI therapy were not shown to be at increased risk for COVID-19, although not sufficient data are available yet. CML patients should continue receiving their TKIs, if they have COVID-19, but drug-drug interactions should always be taken into consideration knowing the fact that both TKIs and the co-medications used for the treatment of SARS-CoV-2 infection all can cause QTc interval prolongation. So close monitoring with serial ECGs is necessary together with prompt and timely dose modifications of these drugs in patients with CML and COVID-19.

KEYWORDS

chronic myeloid leukaemia, COVID-19, drug-drug interaction, QTc prolongation, SARS-CoV-2, tyrosine kinase inhibitor

COMPETING INTERESTS

A.E.E. has received advisory board honorarium from Novartis, and he also received speaker bureau honoraria from Novartis and Bristol-Myers Squibb and Pfizer outside the present study.

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