BTK inhibitors in cancer patients with COVID19: "The winner will be the one who controls that chaos" (Napoleon Bonaparte)

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This study has not been presented previously.

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Translational Relevance: In the setting of the evolving COVID19 pandemic, providers must consider how to optimally manage patients with hematologic malignancy. There is rationale both for and against continuation of BTK inhibitors in patients on these drugs for management of CLL and B-cell lymphomas. Herein, we describe both benefits and risks of BTK inhibitor continuation.

Abstract: As the SARS-CoV-2 (COVID19) pandemic spreads and the number of Bruton's tyrosine kinase inhibitor (BTKi)-treated COVID19 affected patients grows, we must consider the pros and cons of BTKi discontinuation for our patients. In favor of BTKi continuation, BTK plays an active role in macrophage polarization. By modulating key transcription factors, BTK may regulate macrophage polarization downstream of classic M1 and M2 polarizing stimuli and mitigate the hyperinflammatory state associated with COVID19. In favor of BTKi discontinuation, we note a potentially increased risk of secondary infections or impaired humoral immunity. We hypothesize that the potential benefit of blunting a hyper-inflammatory response to SARS-CoV-2 through attenuation of M1 polarization outweighs the potential risk of impaired humoral immunity, not to mention the risk of rapid progression of B-cell malignancy following BTKi interruption. Based on this, we suggest continuing BTKi in patients with COVID19.

Thousands of patients with chronic lymphocytic leukemia (CLL) and B-cell lymphomas are currently treated with Bruton's tyrosine kinase inhibitors (BTKi), including ibrutinib, acalabrutinib and zanubrutinib. As the SARS-CoV-2 (COVID19) pandemic spreads and the number of BTKi-treated COVID19 affected patients grows, we must consider the pros and cons of BTKi discontinuation for these patients. A recent survey of CLL specialists conducted by the CLL Society showed stark disagreement regarding BTKi management. 40% reported that they were in favor of BTKi continuation and 60% reported that they would discontinue BTKi for COVID19 patients or would only continue in certain clinical scenarios.(1) To fully inform this decision, one must consider the potential protective anti-inflammatory effects of BTKis versus the theoretical risk of humoral immunosuppression.

SARS viruses are known to induce a hyperinflammatory state in part through M1 macrophage-associated activity, which not only promotes viral spreading via increased lymphocyte and infected monocyte flux, but also causes massive cell death, depletion of monocytes and macrophage "burn out" leading to the clinical consequences of COVID19.(2) Later stages of COVID19 are similarly marked by systemic hyperinflammation with potentially life-threating cardio-pulmonary collapse and massive cell death.(3) Thus, blunting SARS-CoV-2 induced cytokine storm may be important in mitigating pulmonary, cardiac and vascular system injury. In COVID19, laboratory markers of systemic inflammation (i.e., IFN-γ, IL-2, IL-6, MIP1-α) are elevated, again providing evidence that activation of T-cells and monocytes, with polarization of macrophages to an M1 state is fundamental in this immune dysregulation.(4,5) Targeted immunomodulatory drugs that decrease the M1 macrophage inflammatory response may minimize organ damage by blocking activation of the TH1/M1 inflammatory cascade.

BTK plays an active role in macrophage polarization by regulating transcription factors, such as NF-κB and interferon regulatory factors.(6-10) By modulating these transcription factors, BTK may regulate macrophage polarization downstream of classic M1 and M2 polarizing stimuli.(11) For example, in *BTK* knockout mice, impaired recruitment of M1 macrophages and preferential polarization towards an M2 phenotype support BTK as a key in regulator of M1 polarization. Moreover, BTK deficient macrophages are not only defective in inducing pro-inflammatory cytokines, but preferentially polarize towards anti-inflammatory M2 macrophages, even in response to pro-inflammatory stimuli.(11) Additional preclinical studies have examined the effect of ibrutinib in the setting of influenza A infection. For mice lethally infected with influenza A virus, ibrutinib improved overall survival with resolution of infection, attenuation of lung inflammation, and reduced levels of inflammatory cytokines.(12)

Though these data support the potential utility of BTKi in the setting of COVID19, one also must consider the potentially increased risk of secondary infections or impaired humoral immunity in patients on BTKis. Opportunistic infections, particularly pneumonia, are commonly reported with ibrutinib and other BTKi, with a systematic review showing that 56% of ibrutinib-treated patients experienced an infectious complication.(13) With 3 years of follow-up, 6% of patients receiving first-line ibrutinib and 25% of relapsed/refractory patients receiving ibrutinib developed pneumonia.(14) Ibrutinib has been shown to affect humoral immunity; IgG levels remain stable during the first 12 months of ibrutinib therapy but subsequently fall over time, while IgA levels increase over time.(15,16) During ibrutinib exposure, normal B-cells levels increase but continue to remain abnormally low.(15) These findings are consistent with the clinical observation that the frequency of infections appears to decrease over time, especially after the first 6 months of ibrutinib.(15,16)

The effect of BTKi on the host's ability to develop immunity to SARS-CoV-2 or to a SARS-CoV-2 vaccine must also be considered. Patients with CLL are known to have decreased responses to vaccination; the seroconversion of untreated CLL patients to influenza vaccine is reported in the range of 10-50%.(17-19) Data on the effect of BTKi on vaccine efficacy is limited and mixed. A study of 19 ibrutinib-treated patients demonstrated that 26% (5/19 pts; 95%CI: 9.2-51.2%) seroconverted to at least one strain of influenza following vaccination, a proportion within the range of reported seroconversions in untreated CLL patients.(20) Conversely, two smaller studies suggested that patients treated with BTKi may have inferior vaccine responses (0/13 ibrutinib-treated patients vaccinated for influenza seroconverted,(21) 0/4 ibrutinib treated patients had immune response to PCV13 vs. 4/4 untreated CLL patients.(22) Whether BTKi effects on the humoral immune system prevent the development of immunity to SARS-CoV-2 infection remains to be seen.

In patients who receive BTKi for therapy of B-cell malignancies, we hypothesize that the potential benefit of blunting the hyperinflammatory response to SARS-CoV-2 through attenuation of M1 polarization to mitigate the immediate risk of COVID19-related mortality outweighs the potential medium- to long-term risk of impaired humoral immunity. The risk of rapid progression of B-cell malignancy following interruption further supports the argument for continuation of BTKi. Based on this, we suggest continuing BTKi in patients with COVID19, though practitioners should maintain a low threshold to discontinue in the setting of significant clinical decompensation. Further, toxicity of BTKi, which may vary by agent within the class, should be considered in light of clinical context and COVID19-mediated organ dysfunction. Clinical trials are now underway to test BTKi as potential therapy for COVID19 in patients without B cell malignancies.

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