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COVID-19 infection during blinatumomab therapy: Is safety a dilemma?

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Abstract

Patients with acute lymphoblastic leukemia may be particularly vulnerable to SARS-CoV-2 infection and severe illness. The mainstay of current treatment is the use of blinatumomab in patients with refractory or relapsed B-cell precursor acute lymphoblastic leukemia. We discuss the case of a patient with relapsed acute lymphoblastic leukemia who became positive for SARS-CoV-2 during blinatumomab therapy. There are no formal recommendations on the decision to continue, withhold, or delay blinatumomab treatment in these patients. More studies exploring this issue are warranted, as SARS-CoV-2 is expected to be here to stay.

Keywords

Blinatumomab, precursor cell lymphoblastic leukemia-lymphoma, COVID-19, SARS-CoV-2

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Introduction

Patients with hematological malignancies are prone to SARS-CoV-2 infection[1] and are considered a high-risk population for COVID-19-related severe illness.[2] Patients with acute lymphoblastic leukemia (ALL) may be particularly vulnerable as a consequence of immunosuppression secondary to disease (i.e. low immunoglobulin levels, myelosuppression) and its treatment (i.e. steroid exposure; impaired B-cell response; pulmonary, cardiac, or renal toxicities).[3] Several strategies have been suggested to reduce infection rate and severe illness (e.g. less intensive regimens, transition to outpatient settings for therapy infusion). Thus, each patient-specific context governs the shared-decision making to delay, withhold, reduce or continue treatment.[3]

Blinatumomab is a novel CD3-CD19 bispecific monoclonal antibody that improves overall survival with less toxicity in adult patients with relapsed or refractory B-cell precursor ALL.[4] Its use is expected to induce hypogammaglobulinemia, blunt B-cell response, and impair B-cell-dependent T-cell activation.[5] The most recent consensus of the European Society of Clinical Microbiology and Infectious Diseases on the safety of targeted and biological therapies (2018) reported a significant risk for several infections, including urinary tract and bloodstream infections, invasive fungal infections, cytomegalovirus-related diseases, pneumonia (viral, non-viral, *Pneumocystis jirovecii*), enteroviral encephalitis, and progressive multifocal leukoencephalopathy. To date, there are no specific recommendations concerning SARS-CoV-2 and blinatumomab. Thus, the decision to withhold therapy should balance its risks and benefits.

Should we interrupt blinatumomab therapy in patients who become SARS-CoV-2 positive during treatment? As no recommendation for this scenario is available, we discuss the case of a patient with relapsed ALL who completed blinatumomab therapy without clinical deterioration (Figure 1).

Case

A 47-year-old female patient with a medical history of arterial hypertension, hypothyroidism, and a mild infection by SARS-CoV-2 on December 2020 was diagnosed with common phenotype B precursor ALL, with high risk due to age; an identical Human Leukocyte Antigen (HLA) donor was available. She

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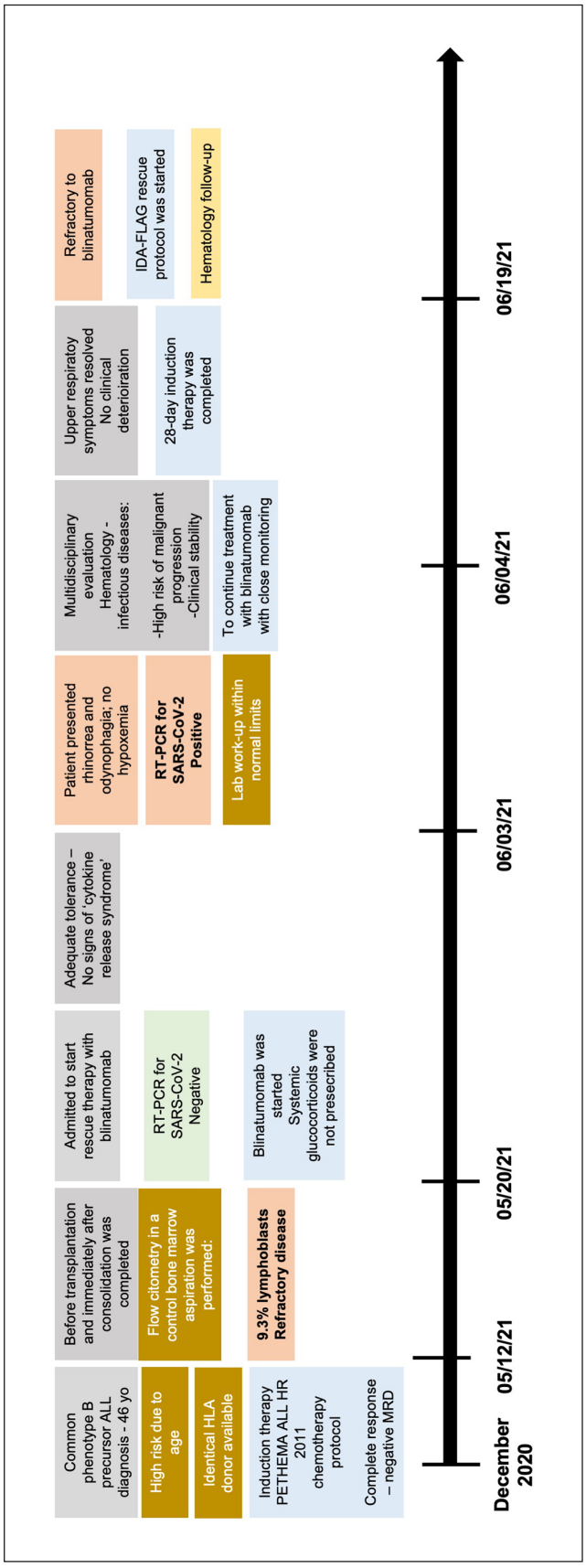

Figure 1. Timeline of COVID-19 infection during blinatumomab therapy for acute lymphoblastic leukemia case.
ALL: Acute Lymphoblastic Leukemia; yo: years old; MRD: Minimal residual disease.

received induction therapy according to PETHEMA ALL HR 2011 chemotherapy protocol,[6] achieving a complete response with negative minimal residual disease. Before transplantation and immediately after consolidation therapy was completed, flow cytometry in a control bone marrow aspiration reported 9.3% of lymphoblasts, compatible with refractory disease. She was admitted on May 2021 to start rescue therapy with blinatumomab. Current medication included acyclovir 400 mg BID, allopurinol 300 mg QD, esomeprazole 40 mg QD, levothyroxine 100 µg QD, and losartan 50 mg BID. Vaccination for SARS-CoV-2 was still unavailable. Physical examination and lab workup on admission were unremarkable. Per institutional protocol, a real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 yielded a negative result. Blinatumomab was started with an adequate tolerance; she did not present signs of cytokine release syndrome, and glucocorticoids were not prescribed. After 2 weeks of in-hospital follow-up, the patient presented with rhinorrhea and odynophagia without hypoxemia; an RT-PCR for SARS-CoV-2 yielded a positive result, lab workup remained within normal limits. A multidisciplinary evaluation by hematology and infectious diseases specialists established a mild case of reinfection due to SARS-CoV-2. Due to the high risk of malignant progression, her clinical stability, and the lack of evidence to support a higher risk for severe illness, the multidisciplinary board decided to continue treatment with blinatumomab with close monitoring; the patient agreed upon it. Upper respiratory symptoms resolved, and the patient completed 28-day induction therapy without clinical deterioration. She was refractory to blinatumomab regarding hematological outcomes, and IDA-FLAG rescue chemotherapy protocol was started.[7]

Discussion

Following international guidelines,[8–10] our patient was screened for SARS-CoV-2 infection before induction with blinatumomab, which was started after a negative test result. During therapy, she became positive and presented mild illness. A hyperinflammatory syndrome known as "cytokine storm" has been implicated as one of the drivers of severe illness in COVID-19.[11]

A similar entity known as "cytokine release syndrome" (CRS) has been associated with the use of blinatumomab. In its pivotal study, 16% of patients in the blinatumomab arm presented a CRS event.[4] Therefore, a theoretical hazard for a higher risk of CRS in patients previously exposed to SARS-CoV-2 has been suggested.[12] Hence, high-dose dexamethasone is considered first-line therapy in cases of CRS and as premedication before initiating blinatumomab therapy to reduce the risk of CRS. In this line, evidence supports dexamethasone's use for COVID-19.[13] Nonetheless, our patient did not receive glucocorticoids; thus, clinical stability during active infection was not associated with their protective effects.

Furthermore, we could not rule out that lack of response to blinatumomab may explain the absence of a CRS event. Based on our experience, we have observed that patients who do not present CRS usually do not achieve remission. This insight from clinical experience should be explored in real-world studies.

Is blinatumomab a safe therapy during SARS-CoV-2 infection? Mounting evidence suggests a higher risk of COVID-19-related severe illness in patients treated with rituximab.[11] However, data supporting the negative influence of other B-cell-depleting therapies, including blinatumomab, is lacking. Due to its mechanism of action, a reduction in immunoglobulin concentration is expected due to the sustained depletion of bone marrow and circulating CD-19+ B-cells.[14] However, current evidence shows that only a small share of patients present overt hypogammaglobulinemia (6%).[4] It would be bold to consider that the absence of severe illness in our patient was associated with a potentially safer risk profile of blinatumomab. We hypothesize that previous SARS-CoV-2 infection conferred natural immunity, as neutralizing antibodies are associated with a lower risk of symptomatic disease.[15] As our patient was refractory to blinatumomab therapy, the depletion of immunoglobulin-producing cells would have been incomplete; this phenomenon was previously suggested in non-respondents.[14] In addition, memory T-cell response against SARS-CoV-2 might have also been preserved.

Conclusion

The mainstay of current treatment is the use of blinatumomab in patients with refractory or relapsed B-cell precursor ALL. These patients present a high risk of progression and unfavorable outcomes if not treated promptly. Therefore, the decision to continue, withhold, or delay blinatumomab treatment in patients who become positive for SARS-CoV-2 during therapy should be approached case-by-case; informed and shared-decision making is encouraged. More studies exploring this issue are warranted, as SARS-CoV-2 is expected to be here to stay.

Author contributions

All authors contributed to the conception and design of the manuscript. Material preparation, data collection, and analysis were performed by J.E.B.-C., C.R.-O., M.-J.L., S.G., and M.A.-Z. J.E.B.-C. and C.R.-O. drafted the manuscript; all authors commented on previous versions. All authors read and approved the final manuscript. We have obtained the required ethical approvals and given the necessary attention to ensure the integrity of the work.

Declaration of conflicting interests

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Ethical approval

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Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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