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Letter to the Editor

Optimal Upfront CLL Treatment during the COVID-19 Pandemic

Ezzat Elhassadi*

University Hospital Waterford, Waterford, Ireland

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Dear Editor,

Here, we report the optimal upfront CLL treatment during the COVID-19 pandemic.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has challenged our healthcare systems and threatened individuals worldwide, particularly the most vulnerable elderly and those with medical comorbidities. The emergence of the new virus variant with its increased infectivity threats requires a quick response before the availability of evidence on managing patients with chronic lymphocytic leukemia (CLL) in this pandemic. Accordingly, this document prepared to provide informed opinions based on available evidence on how CLL patients were treated during the pandemic period.

CLL and COVID-19 Infection Risk

Several factors linked to CLL contribute to the high risk of recurrent infections, including cellular and humoral immune defects (hypogammaglobulinemia, qualitative and quantitative B and T cell defects, CD4+ lymphopenia, innate immune dysfunction, and neutropenia). This immune dysfunction resulted in the impaired immune response to infection and vaccination [1]. These immune defects can be exacerbated further by chemoimmunotherapy (CIT), with an associated risk of viral infections [2]. Thus, exiting and or treatment induce immune dysfunction might also prevent or delay CLL patients' ability to react against the SARS-CoV-2 virus or cope with COVID-19 infection severity.

It is uncertain whether cancer patients, including CLL, have a higher prevalence of COVID-19 infection than matched age and gender normal populations [3]. However, there is accumulating evidence that cancer conveys a more unsatisfactory outcome in patients with COVID-19 infection [4]. CLL is a disease of the elderly population more often associated with pre-existing medical comorbidities, which have a detrimental effect on COVID-19 morbidity and mortality. The typical patient with CLL may already have background risk factors for life-threatening COVID-19 that apply to the general population [4]. Accordingly, around 70% of patients with CLL are male, 70% are older than 65 years, 25% harbour >2 comorbidities, 21% have hypertension, 13% cardiovascular disease, 26% diabetes, and 5% chronic respiratory disease [5].

COVID-19 Infection Prevention Strategy and CLL

Until the COVID-19 vaccine becomes available, public health and non-pharmaceutical interventions aimed at reducing population contact rate and ultimately reducing virus transmission which are the most effective prevention measures for SARS-CoV-2 infection [6]. The spread of SARS-CoV-2 across patients and healthcare professionals is a serious concern and COVID-19 free environments are the ultimate goal for

**Correspondence to: Professor Ezzat Elhassadi, University Hospital Waterford, Dunmore Road, Waterford, Ireland; E-mail: ezzat.elhassadi@hse.ie*

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safely taking care of CLL patients [7]. The same will also imply using treatment options if indicated with less risk of further suppressing the immune systems and requiring less frequent hospital visits during both endemic and future epidemic outbreaks.

Management of CLL Patients Needing Therapy during the Pandemic

Unless specific treatment initiation criteria are met, clinicians should defer the CLL treatment initiation. In general, during the COVID-19 pandemic, commencing of therapy is postponed until the epidemic trajectory is decreasing. When treatment cannot be deferred, we should use the systemic treatment that requires fewer hospital visits and less immune suppressive to reduce the risk of nosocomial SARS-CoV-2 infection. In our practice, only Chemoimmunotherapy (CIT) is licensed in the upfront line setting for most CLL patients (~90%) (lacking p53 gene alterations), while targeted therapies (Ibrutinib & Venetoclax) only approved for patient harbouring p53 disruptions (~10%). With these limitations, CLL treatment during the COVID-19 pandemic has proven to be a challenging task, further complicated with CIT, which increases the risk of infection.

Optimal Upfront CLL Treatment Options during the COVID-19 Pandemic

Ibrutinib as monotherapy for upfront treatment for CLL patients is considered as the ideal if not the best treatment option during the COVID-19 pandemic. The rationale of this recommendation is based on the following evidence:

i. Several well-designed clinical trials confirmed targeted therapies (Ibrutinib & Venetoclax) are associated with prolonged progression-free and overall survival, in comparison with the standard of care (CIT) [8-11].

ii. Ibrutinib therapy is associated with a lower risk of infections and less frequent hospital care than CIT [12]. The reported risk of opportunistic infections for Ibrutinib is low (4.1%), compared favourably to CIT [13]. Also, Ibrutinib does not produce significant lymphopenia, a known risk factor for severe COVID-19 [13].

iii. Ibrutinib treatment requires a few routine hospital visits and lab assessments with low neutropenia risk [12]. It also enhances the T cell immune reconstitution, which decreases the infection rate after the first six months of therapy [12, 14]. Although Ibrutinib is a continuous therapy not allowing treatment-free intervals during the pandemic. However, for patients in remission, treatment interruption for side effects, the achieved response may last for a prolonged period before an alternative therapy is required [15].

iv. Emerging data reporting anti-inflammatory effects in COVID-19 patients using BTK inhibitors are also undergoing investigation in clinical trials (NCT04346199) [16]. By targeting BTK and other kinases and intermediates, Ibrutinib can minimize inflammation and prevent acute lung injury or ARDS and reduce viral replication during the COVID-19 pandemic [17].

v. In CLL patients, the serologic response post-SARS-CoV-2 infection is impaired, and with only one-third of patients developing detectable immunoglobulin G antibodies after a median of ~2 months [18]. This inadequate immune response could be compromised further by CIT and the addition of anti-CD20 monoclonal antibodies. The addition of anti-CD20 monoclonal antibodies failed to improve PFS when combined with Ibrutinib [19]. Therefore, Ibrutinib monotherapy is a less immunosuppressive and very effective treatment without the immune response impact of anti-CD20 monoclonal antibody therapy on COVID-19 infection and vaccination. The CLL research community has already developed a COVID-19/CLL consortium and presented inferior outcomes in this population [20].

According to these considerations and reasons addressed above, we recommend Ibrutinib monotherapy for all CLL patients requiring treatment during the COVID-19 pandemic considering the cost-effectiveness of this approach.

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