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Narrative review

B-cell malignancies and COVID-19: a narrative review

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ABSTRACT

Background: COVID-19 has been extensively characterized in immunocompetent hosts and to a lesser extent in immunocompromised populations. Among the latter, patients treated for B-cell malignancies have immunosuppression generated by B-cell lymphodepletion/aplasia resulting in an increased susceptibility to respiratory virus infections and poor response to vaccination. The consequence is that these patients are likely to develop severe or critical COVID-19.

Objectives: To examine the overall impact of COVID-19 in patients treated for a B-cell malignancy or receiving chimeric antigen receptor T (CAR-T) immunotherapy administered in case of relapsed or refractory disease.

Sources: We searched in the MEDLINE database to identify relevant studies, trials, reviews, or meta-analyses focusing on SARS-CoV-2 vaccination or COVID-19 management in patients treated for a B-cell malignancy or recipients of CAR-T cell therapy up to 8 July 2022.

Content: The epidemiology and outcomes of COVID-19 in patients with B-cell malignancy and CAR-T cell recipients are summarized. Vaccine efficacy in these subgroups is compiled. Considering the successive surges of variants of concern, we propose a critical appraisal of treatment strategies by discussing the use of neutralizing monoclonal antibodies, convalescent plasma therapy, direct-acting antiviral drugs, corticosteroids, and immunomodulators.

Implications: For patients with B-cell malignancy, preventive vaccination against SARS-CoV-2 remains essential and the management of COVID-19 includes control of viral replication because of protracted SARS-CoV-2 shedding. Passive immunotherapy (monoclonal neutralizing antibody therapy and convalescent plasma therapy) and direct-acting antivirals, such as remdesivir and nirmatrelvir/ritonavir are the best currently available treatments. Real-world data and subgroup analyses in larger trials are warranted to assess COVID-19 therapeutics in B-cell depleted populations. David Luque-Paz, Clin Microbiol Infect 2023;29:332 © 2022 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

Introduction

The COVID-19 pandemic started >2 years ago, and its characteristics and outcomes in immunocompetent individuals have been largely described [1]. Although several treatments have been successively approved for the treatment of COVID-19, we still do not have solid evidence-based data regarding the optimal strategy to treat immunocompromised patients. Most treatment guidelines address COVID-19 through disease status (i.e. mild, moderate, or severe) and not sufficiently according to host—immune status [2]. This gap is a consequence of very few inclusions of immunocompromised patients in registered clinical trials [3]. SARS-CoV-2 variants of concern (VOCs) have caused physicians to constantly revisit the management strategies according to retained efficacy of treatments. To date, the VOC Omicron and its sublineages may cause less severe disease in the general population; however, there is uncertainty regarding their impact on the individuals with immune...
deficiency. Recent data suggest escape of these sublineages to vaccine-induced serum levels neutralizing activity suggesting a gain in neutralization resistance over time, of further concern for immunocompromised populations who are less likely to be vaccine responders [4,5].

Thus, it is important to examine the impact of COVID-19 in specific subgroups of immunocompromised populations to improve their practical management throughout the enduring pandemic. Profound humoral deficiency is a risk factor for severe-to-critical COVID-19, and B-cell malignancies (BCMs) are primary providers of this immune dysregulation.

In this narrative review, we intend to provide an overview of the burden of COVID-19 in patients treated for BCMs. Disease-specific series addressing the clinical outcome and the effect of prevention and treatment strategies are important to adapt the management. We searched in the MEDLINE database to identify the most relevant studies, trials, reviews, or meta-analyses until 8 July 2022.

**Immunopathology of COVID-19 in BCMs**

Recent studies have provided insights regarding the immune response to SARS-CoV-2 infection or after vaccination in population having BCMs or receiving B-cell depleting therapy. They have impaired humoral response after vaccination proven by quantitatively and qualitatively lower antibody levels against the SARS-CoV-2 spike protein than that seen in healthy individuals [6,7]. This is of importance considering the link between the kinetics of neutralizing antibodies production and clinical disease outcome. A study conducted in immune competent individuals has shown that those deceased from COVID-19 had delayed neutralizing antibody release in comparison with discharged patients with COVID-19 and ambulatory high neutralizers [8]. A high viral load ($>\log_{10} 5.6/mL$) has been found significantly associated with an increased risk of mortality, and this lethal risk increased by 7% for each $\log_{10}$ increment in a large general population cohort, underscorung the critical role of neutralizing antibodies [9].

Active BCM therapies may also impair specific T-cell response [7]. Nevertheless, T-cell immunity, which is highly correlated with antiviral activity [10], still generates a detectable specific response after vaccination or infection in approximately 3 quarters of the cases [11]. This is indirectly confirmed by the fact that patients with a greater number of CD8+ T cells have an improved survival, regardless of previous anti-CD20+ therapy [11].

**COVID-19 outcomes in BCMs**

The summary of overall clinical outcomes and level of immune responses to SARS-CoV-2 mRNA vaccines in patients with BCM are provided in **Table 1**. Most large multicentre COVID-19 studies have pooled all haematological malignancies together (Table S1). Although there are intrinsic differences, common features exist: (a) an increased risk of severe or fatal COVID-19; (b) risk factors, such as age and aggressive or progressive disease requiring intensive treatment worsen the prognosis [12]; (c) protracted SARS-CoV-2 shedding [13]; and (d) an increased risk of thrombosis in comparison with the general population [14].

**Lymphoma**

Patients with lymphoma were identified early in the pandemic to be at an increased risk of COVID-19, especially those with non-Hodgkin lymphoma (NHL) [15]. Clinical outcomes of patients with NHL and Hodgkin lymphoma (HL) infected with SARS-CoV-2 differ considerably to the advantage of HL [16]. A prognostic model based on a large prospective cohort of 856 patients with lymphoma identified that HL was associated with the best survival, partly explained by younger ages [16]. In NHL, an overall mortality rate ranging from 31% to 35% was reported [17,18]. Among risk factors of mortality, the 2 prominent were age >70 years and relapsed or refractory lymphoma [17,18]. Several cohorts comprising patients with lymphoma found that persistent viral infection >6 weeks was associated with mortality [17,19].

The vaccine response in patients with lymphoma depends on the timing of treatment (Table S2). In off-treatment period, a seroconversion rate as high as 89% has been reported [20]. Seroconversion is found in <10% in case of anti-CD-20+ therapies (rituximab and obinutuzumab) [20]. A significantly enhanced seroconversion rate is associated with >6 months after the last anti-CD-20+ administration [21]. The immunogenicity induced by mRNA vaccines can also be blunted by other chemotherapies, explaining why NHL had a poorer response to vaccines than HL [22]. Importantly, COVID-19 vaccine booster doses in patients with lymphoma partly increases the ability to seroconvert (up to 18–50%) [21] and 69% of patients who were treated with rituximab who lack antibody response had mRNA vaccine-induced T-cell response, arguing for maintaining vaccination in these patients [23].

**Chronic lymphocytic leukaemia**

Chronic lymphocytic leukaemia (CLL) is the most frequent leukaemia and usually affects the older with underlying comorbidities. This is probably why the proportion of severe COVID-19 was dramatically high in the first reported cohorts (up to 80%) [24]. CLL is responsible for a profound immune dysregulation affecting both cellular and humoral functions because peripheral healthy B cells are significantly decreased and 85% of patients with CLL have hypogammaglobulinemia [25]. In 2 multicentre cohort studies, including 198 and 190 patients with CLL, the mortality rates of hospitalized patients were 37% and 36.4%, respectively [24,26]. Of note, Bruton tyrosine kinase inhibitor had no detrimental impact on mortality because of COVID-19 in comparison to the watch-and-wait strategy in the management of CLL [26]. Overall, these mortality rates exceeding 30% decreased during the pandemic to 18% in the most recent data [27]. This reduction is explained by an optimized management of severe COVID-19 and specific T-cell and B-cell immuity in response to vaccination and previous COVID-19 in treatment-naive patients with CLL [27]. The vaccine response in CLL is highly variable, ranging from 73% of seroconversion in treatment-naive patients to 29% and 4% in patients receiving Bruton tyrosine kinase inhibitor and anti-CD-20+ therapies, respectively [28]. Overall, T-cell response was detectable in >60% of patients [27,29].

**Multiple myeloma**

In the early phase of the pandemic, studies focusing on patients with multiple myeloma (MM) infected by SARS-CoV-2 found that in-hospital mortality rates were >30% [30,31]. In a large prospective cohort study, which was conducted during the first year, the highest mortality rate among BCMs was found in MM [32]. In another study conducted later during the pandemic, the highest occurrence of progression towards severe or critical COVID-19 was found in patients with MM, despite the use of neutralizing monoclonal antibodies (NmAbs) [33].

Patients with MM show an exaggerated response to SARS-CoV-2 vaccine, with seroconversion reported in 93% of cases and a T-cell response rate of 61% [34]. Yet, effective mRNA vaccine-induced neutralizing antibodies were lower than the overall seroconversion rates (one third of vaccinated patients with MM lacked detectable serum neutralizing activity) [35]. Reduced
vaccine effectiveness has been observed in individuals who are male, older age, advanced disease, ongoing MM treatments (especially anti-CD28 and anti-BCMA therapies), and hypogammaglobulinemia [34,36].

**CAR-T immunotherapy**

CAR-T cell immunotherapy is administered after lymphodepleting conditioning, which generates long-term B-cell aplasia and hypogammaglobulinemia [37]. In the 2 largest studies reporting clinical outcomes, intensive care unit admission rates were close to 40%, whereas the mortality rates were 43% (n = 13/30) and 41% (n = 23/56), respectively [38,39]. Most patients had underlying relapsed/refractory NHL (86%, n = 74/86). Response to mRNA SARS-CoV-2 vaccines has been assessed in small observational studies of CAR-T cell recipients showing seroconversion rates ranging from 6% to 30% [40-42]. The largest cohort (n = 33) published to date found that T-cell response (42%) was higher than the humoral response (18%), and no clear benefit in vaccine response was found after administering a second booster dose [42].

**Treatment strategies**

Given that most randomized controlled trials (RCTs) have included few immunocompromised patients and mostly conducted during the circulation of SARS-CoV-2 ancestral strain or pre-Omicron variants, the actual management of COVID-19 in the setting of BCMs may be challenging in certain aspects.

**Corticosteroids**

Dexamethasone was the first treatment that showed a reduction of 36% mortality among hospitalized patients with COVID-19 [43]. The rationale was easily understandable as the hyperinflammatory response in lungs triggered by a viral infection potentially leads to acute respiratory distress syndrome. However, corticosteroids impair innate immune pathways, which may add up to the issue of protracted SARS-CoV-2 shedding because of B-cell depletion and T-cell impairment [44]. In BCMs, the benefit of corticosteroids has not been demonstrated. In several observational studies of patients with depleted B cells, corticosteroids had no substantial impact on the outcomes, including survival [19,45,46]. Whether corticosteroids participate in viral persistence in patients with depleted B cells is a key issue, unanswered so far, leading to likely consider their use in combination with an antiviral therapy.

**Other immunomodulators**

Interleukin 6 inhibitors (tocilizumab and sarilumab) and oral Janus kinase inhibitor baricitinib have not been assessed in the immunocompromised patients, although there is a strong recommendation by the WHO guidelines in favour of their use in severe or critical COVID-19 based on platform trial results [2]. In BCMs, we suggest that their use with corticosteroids should be considered individually only after assessment of the benefit-risk balance.

**Convalescent plasma therapy**

There is a rationale for the use of high-titre polyclonal convalescent plasma therapy (CPT) to palliate B-cell defect and to provide the plasma collected during the circulation of the then dominant VOC. The first published series of 17 patients with BCM previously treated with anti-CD20+ therapy who had protracted COVID-19 showed a resolution of symptoms and decrease in SARS-CoV-2 RNAemia in most patients [19]. Then, 2 retrospective cohort studies of patients with BCM hospitalized because of COVID-19 confirmed that CPT was efficient in treating patients and showed a significant reduction in mortality at 30 days and 16 days, respectively, using propensity score analyses [45,47]. Of note, the large randomised, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial, evaluating the impact of CPT on organ support-free days in more than 1000 critically ill patients with COVID-19, although stopped for futility, found a nonsignificant trend for the use of CPTin the subgroup of immunocompromised patients [48]. CPT has been authorized by the U.S. Food and Drug Administration under an emergency use authorization for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment [49]. Overall, in patients with BCM hospitalized with COVID-19 who present with clinically and virologically persistent infection, the use of high-titre CPT, from donors who recently recovered from COVID-19, is among the therapeutic available options. Physicians should be aware of the possibility of an antibody-dependent enhancement defined by enhanced antibody-mediated viral uptake into phagocytic cells, causing immune complex-dependent inflammatory syndrome [50]. Other adverse events, namely, transfusion-associated circulatory overload, transfusion-related acute lung injury or allergic reaction are very uncommon [51].

**Neutralizing monoclonal antibodies**

The use of NmAbs is a relevant approach for immunocompromised patients considered nonresponders to vaccines. A major

### Table 1

| Outcome | Multiple myeloma | Chronic lymphocytic leukaemia | Indolent lymphoma or Hodgkin lymphoma | Non-Hodgkin lymphoma | CAR-T cell recipients |
|---------|-----------------|-----------------------------|-------------------------------------|---------------------|----------------------|
| **Vaccine response** | Good if untreated >90% | Intermediate if untreated ~70% | Good if untreated >90% | Good if untreated >90% | Poor 10-30% |
| **T-cell response** | Intermediate -60% | Intermediate 60-70% | Unknown | Intermediate -70% | Poor ~40% |
| **Clinical outcome** | High >60% Very high | Intermediate <50% | Intermediate >50% | Intermediate <30% | Very high |
| **In-hospital mortality rate** | ~30% | ~30% | ~30% | ~30% | ~30% |

BTKi, Bruton tyrosine kinase inhibitor; CAR-T cell, chimeric antigen receptor T cell.
issue has been the emergence of VOCs requiring constant adjustment according to the retention of efficacy of the available NmAbs. Multiple RCTs evaluating the efficacy of NmAbs at various stages of SARS-CoV-2 infection have confirmed that the best window of opportunity for these treatments to improve patients’ overall outcome was the preexposure or the early postexposure phases in patients at high risk of progression to severe COVID-19 [52–54]. Chronologically, the combination of bamlanivimab and etesevimab was the first to induce a reduction in hospitalization and 29-day mortality versus placebo in the outpatient setting, but was proven to be inactive on Beta and Delta variants [52]. The combination of casirivimab and imdevimab was also found to significantly prevent hospitalization and reduce 28-day mortality versus placebo for outpatients [53] and reduced 28-day mortality among hospitalized patients with COVID-19 who were seronegative at baseline versus standard of care [55]. This combination did not retain efficacy on the Omicron variant [56]. The combination tixagevimab and cilgavimab was reformatted with amino acid substitutions in the Fc regions to extend their serum half-lives and reduce Fcγ receptor and complement binding [57]. Preliminary results of a phase III trial designed to evaluate tixagevimab and cilgavimab as preexposure prophylaxis, which included high-risk and immunocompromised participants, showed a reduced risk of developing symptomatic COVID-19 by 83% versus placebo [58]. Another RCT showed that the administration of tixagevimab and cilgavimab in the early outpatient setting significantly reduced the occurrence of severe COVID-19 or death [59]. Finally, in the setting of patients hospitalized with COVID-19, tixagevimab and cilgavimab reduced by 30% the 90-day mortality versus placebo (secondary outcome), although the RCT was conducted before the Omicron era and failed to achieve sustained clinical recovery (primary outcome) [60]. Sotrovimab was assessed in the treatment of early stages of infection (symptomatic outpatients ≤5 days) that showed a risk reduction of hospitalization or 29-day mortality by 85% versus placebo [54]. Bebtelovimab, a new Omicron-active NmA, has received emergency use authorization by the U.S. Food and Drug Administration for the treatment of mild-to-moderate COVID-19 in outpatients who are at high risk of progression to severe COVID-19, but is not currently available in Europe [61]. Results of neutralizing assays on Omicron sublineages influence treatment strategies. Assays performed on live BA.1 and BA.2 showed differences in activity: sotrovimab and bebtelovimab retained activity against BA.1, whereas tixagevimab, cilgavimab and bebtelovimab retained activity against BA.2 [56,62]. As of today, data of neutralizing assays on BA.2.12.1 and BA.4/BA5 revealed that only bebtelovimab and cilgavimab retained the activity [63,64].

Direct-acting antiviral agents

Direct-acting antivirals (DAAs) are important assets in the management of COVID-19 because they all retain in vitro neutralizing activity against VOCs [63]. In patients hospitalized with COVID-19, the use of remdesivir showed no difference in all-cause mortality and on SARS-CoV-2 viral kinetics in comparison to standard of care [65]. However, remdesivir was associated with a shortened time to recovery in patients with mild-to-moderate COVID-19 in 2 trials mostly including immunocompetent patients [66,67]. In the outpatient setting, a 3-day course of remdesivir resulted in an 87% decrease in the risk of COVID-19 progression, although only 41% of patients were immunocompromised [68]. Despite encouraging preliminary data, disappointing results were obtained with molnupiravir in symptomatic outpatients [69]. The nirmatrelvir/ritonavir, an oral protease inhibitor combination, has shown a reduction of 30% in hospitalization and 89% in mortality leading to authorization for the use of mild-to-moderate COVID-19 in outpatients at high risk of progression to severe COVID-19 [70,71]. In addition, a large retrospective cohort study in the Omicron era identified immunosuppressed patients as one of the subgroups for whom nirmatrelvir/ritonavir use is the most effective to prevent severe COVID-19 or death [72]. Drug-drug interactions are the major limit to its wide-spread use, especially in patients with BCMs who frequently have comedinations. There is a growing interest for combined antiviral strategies, including NmAbs and DAAs in the immunocompromised populations, which warrants further validation by RCTs.

Conclusion

BCM carry a high burden in COVID-19 characterized by high case fatality and poor humoral vaccine-induced response. Nevertheless, vaccinating these patients remains an essential measure of prevention. In these populations at high risk of progression to severe COVID-19, preexposure prophylaxis using NmAbs must be proposed when feasible. The cornerstone of curative treatment is DAAs or variant-active NmAbs for outpatients with mild-to-moderate COVID-19 and NmAbs or high-titre polyclonal CPT in hospitalized patients. Combining antiviral approach may gain interest in the future.

Author contribution

DLP and FA were the project initiators and drafted the manuscript as well as approved the final version. FW, PS, and EB revised the manuscript for important intellectual content and approved the final version.

Transparency declaration

The authors declare that they have no conflicts of interest.

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.10.030.

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