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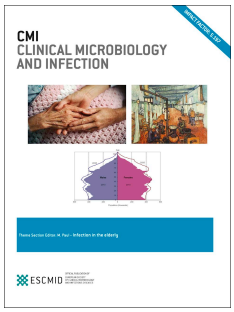

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B-cell malignancies and COVID-19: a narrative review

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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 a higher 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 July 8th, 2022.

Content. The epidemiology and the outcomes of COVID-19 in B-cell malignancy patients 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 B-cell malignancy patients, preventive vaccination against SARS-CoV-2 remain essential and management of COVID-19 includes the control of viral replication due to protracted SARS-CoV-2 shedding. Passive immunotherapy (monoclonal neutralizing antibody therapy, convalescent plasma therapy) and direct-active antivirals such as remdesivir and nirmatrelvir/ritonavir are the best currently available treatments. Real-world data and sub-group analyses in larger trials are warranted to assess COVID-19 therapeutics in B-cell depleted populations.

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic started more than two 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 (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 management strategies according to retained efficacy of treatments. To date, the VOC Omicron and its sub-lineages may cause less severe disease in the general population, but there is uncertainty regarding their impact in individuals with immune deficiency. Recent data suggest escape of these sub-lineages to vaccine-induced serum neutralizing activity suggesting a gain in neutralization resistance over time, of further concern for immunocompromised populations 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 July 8th, 2022.

Immunopathology of COVID-19 in B-cell malignancies

Recent studies have provided insights regarding 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 compared to healthy individuals [6,7]. This is of importance considering the link between the kinetics of production of neutralizing antibodies 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 to discharged COVID-19 patients and ambulatory high neutralizers [8]. A high viral load (> $\log_{10}$ 5.6 per mL) has been found significantly associated with increased risk of mortality, and this lethal risk increased by 7% for each $\log_{10}$ increment in a large general population cohort, underscoring 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 to antiviral activity [10], still generates a detectable specific response after vaccination or infection in nearly three 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 prior anti-CD20+ therapy [11].

COVID-19 outcomes in B-cell malignancies

Summary of overall clinical outcomes and level of immune responses to SARS-CoV-2 mRNA vaccines in BCM patients 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: *i*) an increased risk of severe or fatal COVID-19; *ii)* risk factors such as age and aggressive or progressive disease requiring intensive treatment worsen the prognosis [12], *iii*) protracted SARS-CoV-2 shedding [13], *iv*) an increased risk of thrombosis in comparison to the general population [14].

Lymphoma

Lymphoma patients were identified early in the pandemic to be at higher 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 lymphoma patients 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 two prominent were age > 70 years and relapsed/refractory lymphoma [17,18]. Several cohorts of lymphoma patients found that persistent viral infection > 6 weeks was associated with mortality [17,19].

Vaccine response in lymphoma patients 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 less than 10% in case of anti-CD-20+ therapies (rituximab, obinutuzumab) [20]. A time > 6 months after the last anti-CD-20+ administration is associated with a significantly enhanced seroconversion rate [21]. The immunogenicity induced by mRNA vaccines can also be blunted by other chemotherapies, explaining why NHL had poorer response to vaccines than HL [22]. Importantly, COVID-19 vaccine booster doses in lymphoma patients have been reported to partly increase the ability to seroconvert (up to 18-50%) [21], and 69% of patients treated with rituximab who lack antibody response had a 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 elderly 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 as peripheral healthy B cells are significantly decreased and 85% of CLL patients have

hypogammaglobulinemia [25]. In two multicentre cohort studies including 198 and 190 CLL patients, the mortality rates of hospitalized patients were 37% and 36.4%, respectively [24,26]. Of note, Bruton tyrosine kinase inhibitor (BTKi) had no detrimental impact on mortality due to 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 immunity in response to vaccination and prior COVID-19 in treatment-naïve CLL patients [27]. Vaccine response in CLL has been shown to be highly variable, ranging from 73% of seroconversion in treatment-naïve patients to 29% and 4% in patients receiving BTKi and anti-CD-20+ therapy respectively [28]. Overall, T-cell response was detectable in more than 60% of patients [27,29].

Multiple myeloma (MM)

Early in the pandemics, studies focusing on patients with multiple myeloma (MM) infected by SARS-CoV-2 found an in-hospital mortality rates were over 30% [30,31]. In a large prospective cohort study which took place during the first year, the highest mortality rate among BCMs was found in MM [32]. In another study carried out later in the pandemic, the highest occurrence of progression toward severe or critical COVID-19 was found in MM patients, despite the use of neutralizing monoclonal antibodies (NmAb) [33].

Response to SARS-CoV-2 vaccine is elevated in MM patients, with seroconversion reported in 93% of cases and a T-cell response rate of 61 % [34]. Yet, effective mRNA vaccine-induced neutralizing antibodies have been found to be lower than the overall seroconversion rates (one third of vaccinated MM patients lacked detectable serum neutralizing activity) [35]. Reduced vaccine efficacy has been observed in male, older age, advanced disease, ongoing MM treatments (especially anti-CD38 and anti-BCMA therapies), and hypogammaglobulinemia [34,36].

Chimeric antigen receptor T cell (CAR-T) immunotherapy

CAR-T cell immunotherapy is administered after lymphodepleting conditioning, which generates long-term B-cell aplasia and hypogammaglobulinemia [37]. In the two largest studies reporting clinical outcomes, ICU admission rates were close to 40% while mortality was 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 a 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 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 took place 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 in hospitalized COVID-19 patients [43]. The rationale was easily understandable as the hyper-inflammatory response in lungs triggered by viral infection potentially leads to acute respiratory distress syndrome. But corticosteroids impair innate immune pathways, which may add up to the issue of protracted SARS-CoV-2 shedding due to B-cell depletion and T-cell impairment [44]. In BCMs, the benefit of corticosteroids has not been demonstrated. In several observational studies of B-cell depleted patients, corticosteroids had no substantial impact on the outcomes, including survival [19,45,46]. Whether corticosteroids participate in viral persistence in B-cell depleted

patients is a key issue, unanswered so far, leading to likely consider their use in combination with an antiviral therapy.

Other Immunomodulators

Interleukin (IL)-6 inhibitors (tocilizumab and sarilumab) and oral Janus kinase (JAK) inhibitor baricitinib have not been assessed in the immunocompromised settings although there is a strong recommendation by the World Health Organization 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 plasma collected during the circulation of the then dominant VOC. The first published series of 17 B-cell malignancy patients previously treated by anti-CD20+ therapy who had protracted COVID-19 has shown a resolution of symptoms and decrease of SARS-CoV-2 RNAemia in most patients [19]. Then, two retrospective cohort studies of BCM patients hospitalised with 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 REMAP-CAP trial, evaluating the impact of CPT on organ support-free days in over more than 2000 critically ill COVID-19 patients, although stopped for futility, found a non-significant trend for the use of CPT in the subgroup of immunocompromised patients [48]. CPT has been authorized by the U.S. Food and Drug Administration (FDA) under an emergency use authorization for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment [49]. Overall, in BCM patients hospitalised with COVID-19 presenting clinically and virologically persistent infection, the use of high-titre CPT from

donors having 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 non responders to vaccines. A major issue has been the emergence of VOCs requiring constant adjustment according to retainment 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 pre-exposure or the early post-exposure phases in patients at high risk for 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 casirivimab and imdevimab was also found to significantly prevent hospitalization and reduce 28-day mortality *vs.* placebo for outpatients [53] and reduced 28-day mortality among hospitalized COVID-19 patients who were seronegative at baseline *vs.* 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 pre-exposure prophylaxis, which included high-risk and immunocompromised participants, have showed a reduced risk of developing symptomatic COVID-19 by 83%

vs. placebo [58]. Another RCT has shown 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 hospitalized COVID-19 patients, tixagevimab and cilgavimab reduced by 30% the 90-day mortality *vs*. placebo (secondary outcome), although the RCT was conducted before the Omicron era and failed to achieve sustained clinical recovery (primary outcome) [60]. Sotrovimab has been assessed in the treatment of early stages of infection (symptomatic outpatients $\leq$ 5 days) showing a risk reduction of hospitalization or 29-day mortality by 85% *vs.* placebo [54]. Bebtelovimab, a new Omicron-active NmAb, has received emergency use authorisation by the FDA for the treatment of mild to moderate COVID-19 in outpatients who are at high risk for progression to severe COVID-19, but is not currently available in Europe [61]. Results of neutralizing assays on Omicron sub-lineages 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 and 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 activity [63,64].

Direct-acting antiviral agents

Direct-acting antivirals (DAAs) are important assets in the management of COVID-19 as 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 two 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 4.1% 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 hospitalisation and 89% in mortality leading to authorization of use for mild to moderate COVID-19 in outpatients at high risk for 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 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 co-medications. There is a growing interest for combined antiviral strategies including NmAbs and DAAs in the immunocompromised populations, which warrants further validation by RCTs.

Conclusion

BCMs 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 for progression to severe COVID-19, pre-exposure 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.

Authorship statements

DLP and FA were the project initiators and drafted the manuscript and approved the final version. FW, PS and EB contributed to the revision of the manuscript for important intellectual content and approved the final version.

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Competing interests

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Table 1. Clinical outcomes and immune responses to SARS-CoV-2 mRNA vaccines in patients with B-cell malignancies or receiving CAR-T cell immunotherapy, expressed in percentages according to literature dataset screening.

Aetiology / Outcome	Multiple myeloma	Chronic lymphocytic leukaemia	Indolent lymphoma or Hodgkin lymphoma	Non-Hodgkin lymphoma	CAR-T cell recipients
Vaccine response					
Antibody response	Good > 90%	Intermediate if untreated ~ 70%	Good if untreated > 90%	Good if untreated > 90%	Poor 10-30 %
		Poor if ongoing BTKi 20-30%		Very poor if ongoing anti-CD20 therapy < 10%	
T-cell response	Intermediate ~ 60%	Intermediate 60-70%	Unknown	Intermediate ~ 70%	Poor ~ 40%
Clinical outcome					
Risk of moderate to severe COVID-19	High > 60%	Very high ~ 80%	Intermediate < 50%	High > 50%	High > 50%
In-hospital mortality rate	High ~ 30%	High ~ 30%	Intermediate < 20%	High ~ 30%	Very high ~ 40%

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; COVID-19, coronavirus diseases 2019; CAR-T cell, chimeric antigen receptor T cell.