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

2

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22

23 **Keywords:** B-cell malignancies; B-cell depletion; COVID-19; SARS-CoV-2; mRNA vaccine;
24 neutralizing monoclonal antibody; convalescent plasma therapy.

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26 **Abstract**

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

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

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

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

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

51 **Introduction**

52 The Coronavirus disease 2019 (COVID-19) pandemic started more than two years ago and its
53 characteristics and outcomes in immunocompetent individuals have been largely described [1].
54 Although several treatments have been successively approved for the treatment of COVID-19,
55 we still do not have solid evidence-based data regarding the optimal strategy to treat
56 immunocompromised patients. Most treatment guidelines address COVID-19 through disease
57 status (mild, moderate, or severe) and not sufficiently according to host immune status [2]. This
58 gap is a consequence of very few inclusions of immunocompromised patients in registered
59 clinical trials [3]. SARS-CoV-2 variants of concern (VOCs) have caused physicians to
60 constantly revisit management strategies according to retained efficacy of treatments. To date,
61 the VOC Omicron and its sub-lineages may cause less severe disease in the general population,
62 but there is uncertainty regarding their impact in individuals with immune deficiency. Recent
63 data suggest escape of these sub-lineages to vaccine-induced serum neutralizing activity
64 suggesting a gain in neutralization resistance over time, of further concern for
65 immunocompromised populations less likely to be vaccine responders [4,5].
66 Thus, it is important to examine the impact of COVID-19 in specific subgroups of
67 immunocompromised populations to improve their practical management throughout the
68 enduring pandemic. Profound humoral deficiency is a risk factor for severe to critical COVID-
69 19 and B-cell malignancies (BCMs) are primary providers of this immune dysregulation.
70 In this narrative review, we intend to provide an overview of the burden of COVID-19 in
71 patients treated for BCMs. Disease-specific series addressing the clinical outcome and the effect
72 of prevention and treatment strategies are important to adapt the management. We searched in
73 the MEDLINE database to identify the most relevant studies, trials, reviews, or meta-analyses
74 until July 8th, 2022.

75 **Immunopathology of COVID-19 in B-cell malignancies**

76 Recent studies have provided insights regarding immune response to SARS-CoV-2 infection
77 or after vaccination in population having BCMs or receiving B-cell depleting therapy. They
78 have impaired humoral response after vaccination proven by quantitatively and qualitatively
79 lower antibody levels against the SARS-CoV-2 spike protein compared to healthy individuals
80 [6,7]. This is of importance considering the link between the kinetics of production of
81 neutralizing antibodies and clinical disease outcome. A study conducted in immune competent
82 individuals has shown that those deceased from COVID-19 had delayed neutralizing antibody
83 release in comparison to discharged COVID-19 patients and ambulatory high neutralizers [8].
84 A high viral load ($> \log_{10} 5.6$ per mL) has been found significantly associated with increased
85 risk of mortality, and this lethal risk increased by 7% for each \log_{10} increment in a large general
86 population cohort, underscoring the critical role of neutralizing antibodies [9].

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

92 **COVID-19 outcomes in B-cell malignancies**

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

100 **Lymphoma**

101 Lymphoma patients were identified early in the pandemic to be at higher risk of COVID-19,
102 especially those with non-Hodgkin lymphoma (NHL) [15]. Clinical outcomes of patients with
103 NHL and Hodgkin lymphoma (HL) infected with SARS-CoV-2 differ considerably to the
104 advantage of HL [16]. A prognostic model based on a large prospective cohort of 856
105 lymphoma patients identified that HL was associated with the best survival, partly explained
106 by younger ages [16]. In NHL, an overall mortality rate ranging from 31% to 35% was reported
107 [17,18]. Among risk factors of mortality, the two prominent were age > 70 years and
108 relapsed/refractory lymphoma [17,18]. Several cohorts of lymphoma patients found that
109 persistent viral infection > 6 weeks was associated with mortality [17,19].

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

120 **Chronic lymphocytic leukaemia**

121 Chronic lymphocytic leukaemia (CLL) is the most frequent leukaemia and usually affects the
122 elderly with underlying comorbidities. This is probably why the proportion of severe COVID-
123 19 was dramatically high in the first reported cohorts (up to 80%) [24]. CLL is responsible for
124 a profound immune dysregulation affecting both cellular and humoral functions as peripheral
125 healthy B cells are significantly decreased and 85% of CLL patients have

126 hypogammaglobulinemia [25]. In two multicentre cohort studies including 198 and 190 CLL
127 patients, the mortality rates of hospitalized patients were 37% and 36.4%, respectively [24,26].
128 Of note, Bruton tyrosine kinase inhibitor (BTKi) had no detrimental impact on mortality due to
129 COVID-19 in comparison to the watch-and-wait strategy in the management of CLL [26].
130 Overall, these mortality rates exceeding 30% decreased during the pandemic to 18% in the most
131 recent data [27]. This reduction is explained by an optimized management of severe COVID-
132 19 and specific T-cell and B-cell immunity in response to vaccination and prior COVID-19 in
133 treatment-naïve CLL patients [27]. Vaccine response in CLL has been shown to be highly
134 variable, ranging from 73% of seroconversion in treatment-naïve patients to 29% and 4% in
135 patients receiving BTKi and anti-CD-20+ therapy respectively [28]. Overall, T-cell response
136 was detectable in more than 60% of patients [27,29].

137 **Multiple myeloma (MM)**

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

144 Response to SARS-CoV-2 vaccine is elevated in MM patients, with seroconversion reported in
145 93% of cases and a T-cell response rate of 61 % [34]. Yet, effective mRNA vaccine-induced
146 neutralizing antibodies have been found to be lower than the overall seroconversion rates (one
147 third of vaccinated MM patients lacked detectable serum neutralizing activity) [35]. Reduced
148 vaccine efficacy has been observed in male, older age, advanced disease, ongoing MM
149 treatments (especially anti-CD38 and anti-BCMA therapies), and hypogammaglobulinemia
150 [34,36].

151 Chimeric antigen receptor T cell (CAR-T) immunotherapy

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

161 Treatment strategies

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

166 Corticosteroids

167 Dexamethasone was the first treatment that showed a reduction of 36% mortality in hospitalized
168 COVID-19 patients [43]. The rationale was easily understandable as the hyper-inflammatory
169 response in lungs triggered by viral infection potentially leads to acute respiratory distress
170 syndrome. But corticosteroids impair innate immune pathways, which may add up to the issue
171 of protracted SARS-CoV-2 shedding due to B-cell depletion and T-cell impairment [44]. In
172 BCMs, the benefit of corticosteroids has not been demonstrated. In several observational studies
173 of B-cell depleted patients, corticosteroids had no substantial impact on the outcomes, including
174 survival [19,45,46]. Whether corticosteroids participate in viral persistence in B-cell depleted

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

177 *Other Immunomodulators*

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

184 *Convalescent plasma therapy*

185 There is a rationale for the use of high-titre polyclonal convalescent plasma therapy (CPT) to
186 palliate B-cell defect and to provide plasma collected during the circulation of the then
187 dominant VOC. The first published series of 17 B-cell malignancy patients previously treated
188 by anti-CD20+ therapy who had protracted COVID-19 has shown a resolution of symptoms
189 and decrease of SARS-CoV-2 RNAemia in most patients [19]. Then, two retrospective cohort
190 studies of BCM patients hospitalised with COVID-19 confirmed that CPT was efficient in
191 treating patients and showed a significant reduction in mortality at 30 days and 16 days
192 respectively using propensity score analyses [45,47]. Of note, the large REMAP-CAP trial,
193 evaluating the impact of CPT on organ support-free days in over more than 2000 critically ill
194 COVID-19 patients, although stopped for futility, found a non-significant trend for the use of
195 CPT in the subgroup of immunocompromised patients [48]. CPT has been authorized by the
196 U.S. Food and Drug Administration (FDA) under an emergency use authorization for the
197 treatment of COVID-19 in patients with immunosuppressive disease or receiving
198 immunosuppressive treatment [49]. Overall, in BCM patients hospitalised with COVID-19
199 presenting clinically and virologically persistent infection, the use of high-titre CPT from

200 donors having recently recovered from COVID-19 is among the therapeutic available options.
201 Physicians should be aware of the possibility of an antibody-dependent enhancement defined
202 by enhanced antibody-mediated viral uptake into phagocytic cells causing immune complex-
203 dependent inflammatory syndrome [50]. Other adverse events, namely transfusion-associated
204 circulatory overload, transfusion-related acute lung injury or allergic reaction are very
205 uncommon [51].

206 *Neutralizing monoclonal antibodies*

207 The use of NmAbs is a relevant approach for immunocompromised patients non responders to
208 vaccines. A major issue has been the emergence of VOCs requiring constant adjustment
209 according to retainment of efficacy of the available NmAbs. Multiple RCTs evaluating the
210 efficacy of NmAbs at various stages of SARS-CoV-2 infection have confirmed that the best
211 window of opportunity for these treatments to improve patients' overall outcome was the pre-
212 exposure or the early post-exposure phases in patients at high risk for progression to severe
213 COVID-19 [52–54]. Chronologically, the combination of bamlanivimab and etesevimab was
214 the first to induce a reduction in hospitalization and 29-day mortality *versus* placebo in the
215 outpatient setting, but was proven to be inactive on Beta and Delta variants [52]. The
216 combination casirivimab and imdevimab was also found to significantly prevent hospitalization
217 and reduce 28-day mortality *vs.* placebo for outpatients [53] and reduced 28-day mortality
218 among hospitalized COVID-19 patients who were seronegative at baseline *vs.* standard of care
219 [55]. This combination did not retain efficacy on the Omicron variant [56]. The combination
220 tixagevimab and cilgavimab was reformatted with amino acid substitutions in the Fc regions to
221 extend their serum half-lives and reduce Fc γ receptor and complement binding [57].
222 Preliminary results of a phase III trial designed to evaluate tixagevimab and cilgavimab as
223 pre-exposure prophylaxis, which included high-risk and immunocompromised
224 participants, have showed a reduced risk of developing symptomatic COVID-19 by 83%

225 vs. placebo [58]. Another RCT has shown that the administration of tixagevimab and
226 cilgavimab in the early outpatient setting significantly reduced the occurrence of severe
227 COVID-19 or death [59]. Finally, in the setting of hospitalized COVID-19 patients,
228 tixagevimab and cilgavimab reduced by 30% the 90-day mortality vs. placebo (secondary
229 outcome), although the RCT was conducted before the Omicron era and failed to achieve
230 sustained clinical recovery (primary outcome) [60]. Sotrovimab has been assessed in the
231 treatment of early stages of infection (symptomatic outpatients ≤ 5 days) showing a risk
232 reduction of hospitalization or 29-day mortality by 85% vs. placebo [54]. Bebtelovimab, a new
233 Omicron-active NmAb, has received emergency use authorisation by the FDA for the treatment
234 of mild to moderate COVID-19 in outpatients who are at high risk for progression to severe
235 COVID-19, but is not currently available in Europe [61]. Results of neutralizing assays on
236 Omicron sub-lineages influence treatment strategies. Assays performed on live BA.1 and BA.2
237 showed differences in activity: sotrovimab and bebtelovimab retained activity against BA.1,
238 whereas tixagevimab and cilgavimab and bebtelovimab retained activity against BA.2 [56,62].
239 As of today, data of neutralizing assays on BA.2.12.1 and BA.4/BA5 revealed that only
240 bebtelovimab and cilgavimab retained activity [63,64].

241 ***Direct-acting antiviral agents***

242 Direct-acting antivirals (DAAs) are important assets in the management of COVID-19 as they
243 all retain *in vitro* neutralizing activity against VOCs [63]. In patients hospitalized with COVID-
244 19, the use of remdesivir showed no difference in all-cause mortality and on SARS-CoV-2 viral
245 kinetics in comparison to standard of care [65]. However, remdesivir was associated with a
246 shortened time to recovery in patients with mild-to-moderate COVID-19 in two trials mostly
247 including immunocompetent patients [66,67]. In the outpatient setting, a 3-day course of
248 remdesivir resulted in an 87% decrease in the risk of COVID-19 progression, although only
249 4.1% of patients were immunocompromised [68]. Despite encouraging preliminary data,

250 disappointing results were obtained with molnupiravir in symptomatic outpatients [69]. The
251 nirmatrelvir/ritonavir, an oral protease inhibitor combination, has shown a reduction of 30% in
252 hospitalisation and 89% in mortality leading to authorization of use for mild to moderate
253 COVID-19 in outpatients at high risk for progression to severe COVID-19 [70,71]. In addition,
254 a large retrospective cohort study in the Omicron era identified immunosuppressed patients as
255 one of the subgroups for whom nirmatrelvir/ritonavir use is most effective to prevent severe
256 COVID-19 or death [72]. Drug-drug interactions are the major limit to its wide-spread use,
257 especially in patients with BCMs who frequently have co-medications. There is a growing
258 interest for combined antiviral strategies including NmAbs and DAAs in the
259 immunocompromised populations, which warrants further validation by RCTs.

260 **Conclusion**

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

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269 DLP and FA were the project initiators and drafted the manuscript and approved the final
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271 content and approved the final version.

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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.