Received: 30 May 2022 | Accepted: 22 July 2022

DOI: 10.1111/bjh.18396

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Impact of severe acute respiratory syndrome coronavirus-2 infection on the outcome of primary central nervous system lymphoma treatment: A study of the International PCNSL Collaborative Group

Sara Steffanoni[1] | Teresa Calimeri[1] | Alice Laurenge[2] | Christopher P. Fox[3] | Carole Soussain[4] | Christian Grommes[5] | Maria Chiara Tisi[6] | Jesca Boot[7] | Nicola Crosbie[8] | Carlo Visco[9] | Luca Arcaini[10] | Sridhar Chaganti[11] | Marianna C. Sassone[1] | Alvaro Alencar[12] | Daniele Armiento[13] | Ilaria Romano[14] | Jorg Dietrich[15] | Gilad Itchaki[16] | Riccardo Bruna[17] | Nicola S. Fracchiolla[18] | Laura Arletti[19] | Adriano Venditti[20] | Stephen Booth[21] | Pellegrino Musto[22] | Khê Hoang Xuan[2] | Tracy T. Batchelor[23] | Kate Cwynarski[24] | Andrés J. M. Ferreri[1]

[1]Lymphoma Unit, Department of Onco-Hematology, IRCCS San Raffaele Scientific Institute, Milan, Italy

[2]Service de Neurologie 2-Mazarin, Hôpitaux Universitaires La Pitié Salpêtrière, APHP, Sorbonne Université, Paris, France

[3]Hematology Department, University Hospitals NHS Trust, Nottingham, UK

[4]Hôpital René Huguenin-Institut Curie, Saint-Cloud, Paris, France

[5]Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, New York, USA

[6]Division of Hematology, Ospedale San Bortolo, Vicenza, Italy

[7]Barking, Havering and Redbridge University Hospitals NHS Trust, London, UK

[8]Derriford Hospital, Plymouth, UK

[9]Department of Medicine, Section of Hematology, University of Verona, Verona, Italy

[10]Division of Hematology, Fondazione IRCCS Policlinico San Matteo and Department of Molecular Medicine, University of Pavia, Pavia, Italy

[11]Department of Haematology, Queen Elizabeth Hospital, Birmingham, UK

[12]Department of Hematology and Oncology, University of Miami/Sylvester Comprehensive Cancer Center, Miami, Florida, USA

[13]Division of Hematology, Campus Bio Medico, Rome, Italy

[14]Division of Hematology, Ospedale Careggi, Florence, Italy

[15]Division of Neuro-Oncology, Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA

[16]Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah-Tikva, Israel

[17]Division of Hematology, Ospedale Maggiore, Novara, Italy

[18]UOC Ematologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[19]Division of Hematology, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy

[20]Department of Biomedicine and Prevention, University Tor Vergata, Rome, Italy

[21]NIHR Oxford Biomedical Research Centre, Churchill Hospital, Oxford, UK

[22]Department of Emergency and Organ Transplantation, 'Aldo Moro' University School of Medicine, and Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari, Italy

[23]Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts, USA

[24]Department of Haematology, University College London Hospital, London, UK

Sara Steffanoni and Teresa Calimeri contributed equally.

Kate Cwynarski and Andrés J. M. Ferreri shared senior author position.

Correspondence
Andrés J. M. Ferreri, Lymphoma Unit, Department of Onco-Hematology, IRCCS San Raffaele Scientific Institute, Via Olgettina 60 – 20132 Milan, Italy.
Email: ferreri.andres@hsr.it

Summary

To optimise management of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection identifying high-risk patients and maintaining treatment dose intensity is an important issue in patients with aggressive lymphomas. In the present study, we report on the presentation, management, and outcome of an international series of 91 patients with primary central nervous system lymphoma and SARS-CoV-2 infection. SARS-CoV-2 was diagnosed before/during first-line treatment in 64 patients, during follow-up in 21, and during salvage therapy in six. Among the 64 patients infected before/during first-line chemotherapy, 38 (59%) developed pneumonia and 26 (41%) did not clear the virus. Prolonged exposure to steroids before viral infection and/or treatment with high-dose cytarabine favoured pneumonia development and virus persistence and were associated with poorer survival; 81% of patients who did not clear virus died early from coronavirus disease 2019 (COVID-19). Vaccination was associated with lower pneumonia incidence and in-hospital mortality. Chemotherapy was initiated/resumed in 43 (67%) patients, more commonly among patients who did not develop pneumonia, cleared the virus, or did not receive steroids during infection. Chemotherapy resumption in patients with viral persistence should be indicated cautiously as it was associated with a poorer survival (6-month, 70% and 87%, $p = 0.07$). None of the 21 patients infected during follow-up died from COVID-19, requiring similar measures as infected subjects in the general population.

KEYWORDS
coronavirus disease 2019 (COVID-19), pneumonia, primary central nervous system lymphoma, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), steroid therapy, vaccine

INTRODUCTION

Since the start of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, the global cumulative number of cases all over the world has reached >512 million, with >6.2 million cases of deaths as of 5 May 2022 (World Health Organization, 2022). Patients with SARS-CoV-2 infection and a diagnosis of cancer are at high risk of severe symptomatic disease (coronavirus disease 2019 [COVID-19]) and death, and cancer is an independent adverse prognostic factor on COVID-19-related mortality.[1] Importantly, effects of SARS-CoV-2 infection across different patient subgroups are uncertain, and wide variability seems to exist according to different tumour types and anti-cancer treatments.[2–4] However, the relatively small sample size of most reports, their retrospective design, and the restriction to hospitalised patients represent important limitations to interpret and compare the reported mortality rates, and the extent to which they can be extrapolated to the wider population of patients with solid or haematological malignancies.

Lymphomas are the most common haematological malignancies diagnosed in patients infected by SARS-CoV-2, and patients with aggressive non-Hodgkin lymphomas represent one of the most vulnerable populations in this setting.[5,6] Several scientific societies have published recommendations for the management of patients with lymphoma during the COVID-19 pandemic in an effort to ensure continuity of cancer care maintaining a balance between risk and benefit.[7–9] During the pandemic, several centres changed clinical practice to attempt to optimise clinical benefit while minimising toxicity, viral exposure risk and resource utilisation.[10–12] For instance, prolonged exposure to anti-CD20 therapy, intensified chemotherapy regimens and some biological drugs were avoided or not recommended to decrease iatrogenic immunosuppression. However, these recommendations should be applied with caution as non-Hodgkin lymphomas consist of a large group of neoplasms with variable biological characteristics, clinical behaviour, and immunological status, requiring diverse treatments.

The effect of the SARS-CoV-2 pandemic on management and outcome of specific lymphoma entities have rarely been reported,[13–15] with an absence of robust evidence to support therapeutic choices in this setting. Patients with primary diffuse large B-cell lymphoma of the central nervous system (PCNSL) represent a challenging population, with distinctive characteristics, and marked frailty, which could predispose to severe complications and high mortality in the case of SARS-CoV-2 infection. Patients with PCNSL often

have poor neurological status and performance status, and are exposed to prolonged therapy with steroids, resulting in metabolic disorders and severe immunosuppression. This highly aggressive tumour requires dose-intensive therapy, especially in young patients who often undergo autologous stem cell transplantation (ASCT). In the only available series of 13 patients with PCNSL, severe forms of SARS-CoV-2 infection occurred in 39% of cases, with a mortality rate of 23%.[16] However, the effects of infection on patients with PCNSL in terms of severe complications, hospitalisation, intensive care unit (ICU) admission, interruption, and delay of anti-tumour treatment and mortality remain to be defined in a large cohort.

Thus, we analysed clinical presentation, prognosis, and effects on tumour treatment and outcome of SARS-CoV-2 infection in a series of 91 patients with PCNSL treated at 27 cancer centres in five countries. The considered cohort started in the pre-vaccination era but includes 16 vaccinated patients. This study, performed under the sponsorship of the International PCNSL Collaborative Group (IPCG), suggests that multidisciplinary strategy facilitates eradication of viral infection and completion of planned tumour therapy, with acceptable timing and short-term survival rate. Results in patients infected with SARS-CoV-2 at time of initial lymphoma diagnosis, relapse, or follow-up, and during the different pandemic waves are discussed separately.

PATIENTS AND METHODS

Study population

This is a multicentre retrospective observational study performed in 27 cancer centres of five countries (France, Israel, Italy, UK, and USA). Members of the IPCG were invited to provide clinical data of adults with diagnosis of PCNSL according to the World Health Organization (WHO) 2017 classification, with concurrent detection of SARS-CoV-2 infection by nasopharyngeal swab samples or by bronchoalveolar lavage. Nasopharyngeal swabs for SARS-CoV-2 diagnosis were managed according to national recommendations. Patients with viral polymerase chain reaction negative but high clinical suspicion and later evidence of antibody seropositivity were considered. Patients with secondary CNS lymphoma were excluded. Patients with PCNSL at initial diagnosis, during first-line or salvage treatment, and during follow-up were considered. Patients were grouped in first, second and third pandemic waves using the 31 July 2020 and 1 January 2021, as cut-offs for SARS-CoV-2 diagnosis. Written informed consent was obtained from each participating patient or by a legal representative of patients who lacked capacity due to their lymphoma. This trial conformed to the Declaration of Helsinki and was approved by the Institutional Review Boards of the participating institutions.

Data on patient characteristics and outcomes were extracted by study investigators from electronic medical records or clinical charts including age, sex, comorbidity previously reported as related to higher COVID-19 severity,[17,18] status of lymphoma and time since diagnosis of PCNSL to SARS-CoV-2 detection. Details of treatment of PCNSL, such as tolerability and dose intensity, treatment delay, interruption, anti-tumour response, relapse rate and mortality were considered. Response to lymphoma treatment was defined according to the IPCG criteria.[19] Other investigated parameters were time to achieve viral clearance (achievement of nasopharyngeal swab negativity), duration of hospitalisation, ICU admission, complications of SARS-CoV-2 infection, performed anti-COVID-19 vaccinations, and serology tests. The value of these variables in predicting the COVID-19 severity and outcome and the role of antiviral, anticoagulant and steroid therapies were also investigated.

Statistics

The primary outcomes were mortality among patients with PCNSL with COVID-19 and evaluation of potential predictive parameters of mortality and COVID-19 severity. Secondary outcomes were lymphoma evolution, viral clearance rate, incidence of pneumonia, factors related to pneumonia and viral persistence, and anti-lymphoma treatment intensity. Clinical characteristics and response rates of the analysed subgroups and factors potentially conditioning pneumonia and viral clearance were compared using the chi-square test or Fisher's exact test for categorical variables, according to the sample size. Time to achieve viral clearance assessed by nasopharyngeal swab was estimated from the date of first positive viraemia to the date of achieving negative viraemia, or of symptoms resolution if a swab was not repeated to confirm virus eradication. Survival curves were generated by the Kaplan–Meier method. Overall survival (OS) was calculated from the date of SARS-CoV-2 detection to death or to the last date of follow-up. Survival rates were reported as 1-, 6- and 12-month OS with 95% confidence intervals (CIs). Impact on survival of clinical and therapeutic variables was evaluated by comparing the entire OS curves by means of the log-rank test. The independent prognostic value of variables was analysed using the Cox model. All the probability values were two-sided. Analyses were carried out using the Statistica 10.0 statistical package for Windows (Statsoft Inc., 1993, Tulsa, OK, USA).

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

RESULTS

Study population

A total of 91 patients were registered between March 2020 and March 2022. The database lock for the present analysis was 25 April 2022. The patients' characteristics are summarised in Table 1. SARS-CoV-2 infection was confirmed

TABLE 1 Patients' characteristics

Variable	Whole series (n = 91)	Vaccinated patients (n = 16)
Age, years, median (range)	66 (22–85)	58 (33–83)
Male/female ratio	1.11	1.66
Race: Caucasian/African/Asiatic/Hispanic, n	81/3/2/5	13/1/0/2
ECOG Performance status at PCNSL diagnosis, n (%)		
0	8 (9)	2 (13)
1	45 (49)	11 (69)
2	15 (16)	1 (6)
3	16 (17)	2 (13)
4	6 (7)	0 (0)
Unknown	1 (1)	
Disease site, n (%)		
Brain parenchyma	75 (82)	12 (75)
Brain + meninges	8 (9)	2 (13)
Brain + eyes	3 (3)	1 (6)
Brain + meninges + eyes	2 (2)	1 (6)
Brain + spinal cord	1 (1)	0 (0)
Meninges alone	1 (1)	0 (0)
Eyes alone	1 (1)	0 (0)
IELSG risk, n (%)		
Low	14 (15)	7 (44)
Intermediate	40 (44)	8 (50)
High	21 (23)	0 (0)
Undefined	16 (18)	1 (6)
Comorbidity, n (%)		
High blood pressure	34 (37)	6 (38)
Hypercholesterolaemia	10 (10)	3 (19)
Vasculopathy/coronaropathy/cardiac arrhythmia	24 (26)	3 (19)
Obesity/overweight	12 (13)	0 (0)
Type 2 diabetes	11 (12)	0 (0)
Chronic respiratory disease	7 (8)	0 (0)
Renal failure	5 (6)	0 (0)
Hepatitis virus infection	7 (8)	0 (0)
HIV	3 (4)	0 (0)
Prior solid or haematological tumour	6 (7)	1 (6)
Autoimmune disorders	4 (5)	0 (0)
None	24 (26)	7 (44)
SARS-CoV-2 detected, n (%)		
Before first-line treatment for PCNSL	14 (15)	0 (0)
During first-line treatment for PCNSL	50 (55)	14 (88)
During follow-up	21 (23)	1 (6)
During salvage treatment (relapsed PCNSL)	6 (7)	1 (6)
Median (range) time between PCNSL and SARS-CoV-2 diagnoses		
Patients infected before first-line therapy (n = 14), days	2 (–27 to +66)	-
Patients infected during first-line therapy (n = 50), days	62 (2–314)	-
Patients infected during relapse (n = 7) or follow-up, months	24 (7–133)	-

TABLE 1 (Continued)

Variable	Whole series (n = 91)	Vaccinated patients (n = 16)
COVID-19 symptoms, *n* (%)		
Fever	37 (41)	5 (31)
Cough	25 (27)	4 (25)
Dyspnea	23 (25)	1 (6)
Fatigue	14 (15)	1 (6)
Pain/headache	1 (1)	0 (0)
Anosmia	2 (3)	0 (0)
Ageusia	1 (1)	1 (6)
Diarrhoea	2 (3)	0 (0)
None	36 (40)	8 (50)
Treatment of COVID-19 (single drugs or combinations), *n* (%)		
Hydroxychloroquine	13 (14)	0 (0)
Hyper-immune plasma	11 (12)	0 (0)
Remdesevir	11 (12)	3 (19)
Sotrovimab	5 (6)	5 (31)
Darunavir/cobicistat	4 (5)	0 (0)
Casirivimab/imdevimab	2 (3)	2 (13)
Tixagévimab/cilgavimab	2 (3)	2 (13)
Molnupiravir	1 (2)	0 (0)
Anakinra	1 (2)	0 (0)
Dexamethasone (range of dose: 4–12 mg/day)	39 (43)	8 (50)
Anticoagulant therapy or prophylaxis	44 (48)	9 (56)
Planed or performed first-line treatment for PCNSL[a,b], *n* (%)		
MPV (± rituximab)[c]	40 (44)	11 (69)
MATRix	28 (31)	1 (6)
PRIMAIN	7 (8)	0 (0)
Methotrexate monotherapy (± rituximab)	7 (8)	3 (19)
Methotrexate-cytarabine (± rituximab)	4 (4)	0 (0)
Rituximab-lenalidomide	1 (1)	0 (0)
Intravitreous chemotherapy alone	1 (1)	0 (0)
None	3 (3)	1 (6)

Abbreviations: COVID-19, coronavirus disease 2019; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; IELSG, International Extranodal Lymphoma Study Group; PCNSL, primary central nervous system lymphoma; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

MVP = methotrexate, vincristine, and procarbazine, followed by high-dose cytarabine ±high-dose etoposide.[20]

PRIMAIN = methotrexate, procarbazine and rituximab.[21]

MATRix = methotrexate, cytarabine, thiotepa, and rituximab.[22]

[a]Treatment of the 50 patients infected during first-line treatment included rituximab in 48, whereas two patients treated were treated with high-dose methotrexate (HD-MTX) alone or MVP regimen without rituximab. Rituximab-containing regimens consisted of MATRix in 18 patients, R-MVP in 19, PRIMAIN in four, R-MVP plus ibrutinib in one, R-MVP plus lenalidomide in one, HD-MTX plus rituximab in four and rituximab-lenalidomide followed by lenalidomide maintenance in one.

[b]First-line treatment for patients infected during follow-up consisted of R-MPV in 13 patients, R-MBVP in two and MATRix in six; followed by consolidation in 15 (whole-brain radiotherapy in four, autologous stem cell transplantation in five, high-dose cytarabine in six).

[c]One patient received lenalidomide, and one patient received ibrutinib.

by molecular examination on samples collected by nasopharyngeal swab or bronchoalveolar lavage in the 91 considered patients. In all, 37 patients were diagnosed during the first pandemic wave, 21 at the second and 33 at the third. SARS-CoV-2 was diagnosed before/during first-line PCNSL treatment in 64 (70%) patients, during relapse of PCNSL in six (7%), and during follow-up in 21 (23%; Table 1). SARS-CoV-2 was diagnosed before/during first-line treatment in 24 (65%), 16 (76%) and 24 (73%) patients of the three considered waves. Importantly, SARS-CoV-2 infection was diagnosed in 16 previously vaccinated patients (Table 1) and in 68 unvaccinated patients; information on COVID-19 vaccination was lacking in seven patients. In all, 13 of these patients received three doses of vaccine, with a median (range)

interval between date of last vaccine dose and SARS-CoV-2 detection of 27 (6–181) days.

SARS-CoV-2 infection at diagnosis or during first-line PCNSL treatment

A SARS-CoV-2 infection was diagnosed before starting first-line treatment PCNSL (before or after PCNSL diagnosis) in 14 patients, with a median (range) time between SARS-CoV-2 detection and first day of lymphoma treatment of 34 (4–69) days; three of these patients never started chemotherapy because they died early from COVID-19. SARS-CoV-2 infection was diagnosed after the first day of first-line PCNSL treatment in 50 patients; lymphoma treatment of these 50 patients is reported in the footnote of Table 1.

In all, 38 (59%) of the 64 patients with a diagnosis of SARS-CoV-2 infection before/during first-line chemo-immunotherapy developed pneumonia (Figure 1), were hospitalised, and nine of them were admitted to ICU. The median (range) interval between first positive swab and pneumonia diagnosis was 2 (1–51) days. Pneumonia was more common amongst unvaccinated patients, patients who received steroid therapy before viral infection for >2 weeks or with a cumulative dose (dexamethasone) of >100 mg, and in patients who received high-dose cytarabine, as induction or consolidation, before viral infection (Table 2). Notably, 22 (71%) of the 31 patients who received >2 weeks of steroids and/or a cumulative dose of >100 mg, and 10 of the 12 patients treated with steroids for 1 month or more developed pneumonia.

The 38 patients with pneumoniae remained hospitalised for a median (range) of 18 (3–192) days, whereas 11 (42%) of the 26 patients without pneumonia required hospitalisation for a median (range) of 21 (2–55) days. Regardless of pneumonia development, antiviral therapy was delivered to 28 patients (Table 1). Nine patients were admitted to ICU, for a median (range) stay of 21 (3–96) days; three of them were managed with invasive ventilation. The nine patients were discharged from the ICU, but five of them died from COVID-19 within 25 days from virus detection.

In all, 18 of the 38 patients with pneumonia cleared the virus (Figure 1); 15 of them resumed anti-lymphoma treatment, whereas consolidation ASCT was delayed in other three patients. At the last visit 17 of these patients were alive (median [range] follow-up 244 [25–534] days). Conversely, 15 of the 20 patients with pneumonia who did not clear virus interrupted chemotherapy (Figure 1); the other five patients received further chemotherapy despite persistent virus detection: three of them died from COVID-19-related

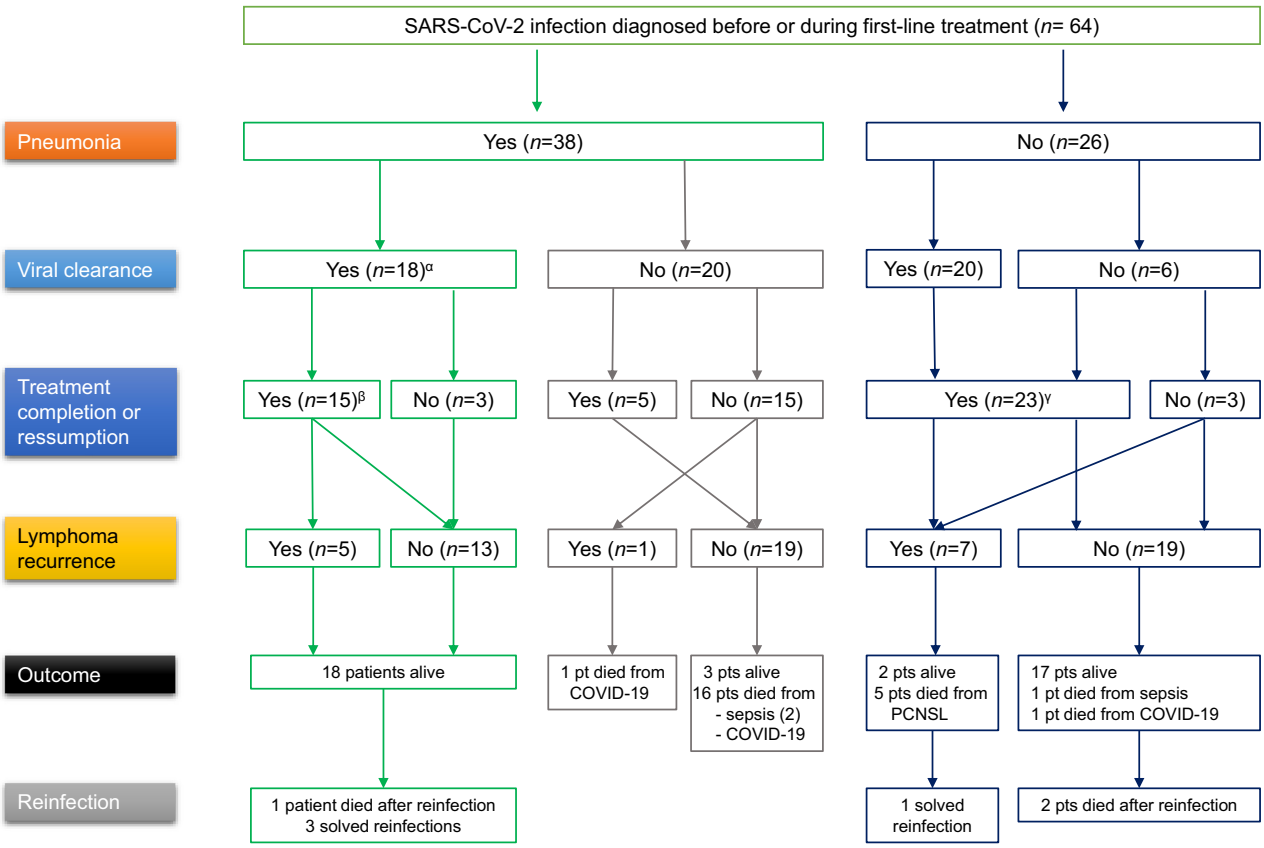

FIGURE 1 Flow chart of the 64 patients with viral detection before or during first-line treatment for lymphoma. [α]Median (range) time to viral clearance of 28 (1–96) days; [β]Median (range) treatment delay of 30 (6–116) days; [γ]Median (range) treatment delay of 19 (0–80) days. COVID-19, coronavirus disease 2019; PCNSL, primary central nervous system lymphoma; pt(s), patient(s); SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

complications and treatment is ongoing in the other two. Overall, 17 of the 20 patients with pneumonia who did not clear virus died from COVID-19 or related infections, within 1 month from SARS-CoV-2 detection (Figure 1). In all, 17 of the 38 patients with pneumonia who required hospitalisation died before discharge; all of them died from COVID-19-related complications; the other 21 patients were discharged. Mortality among patients with pneumonia was significantly lower amongst vaccinated patients, patients with limited pre-COVID-19 exposure to steroids, and those who achieved viral clearance (Table 2).

Among the 26 patients who did not develop pneumonia (Figure 1), 20 cleared the virus and resumed/initiated anti-lymphoma treatment; three of the six patients who did not clear virus initiated/resumed chemotherapy, whereas the other three never initiated treatment. In all, 17 of the 26 patients who did not develop pneumonia patients are alive at 24–419 days (Figure 1), five died from PCNSL, one died from chemotherapy toxicity (sepsis), one died from COVID-19, and two died from COVID-19 reinfection.

Overall, 38 (59%) of the 64 patients with SARS-CoV-2 infection detected during/before first-line treatment cleared the virus (median [range] 26 [1–96] days); 32 (84%) of these patients are alive at a median (range) follow-up of 153 (24–534) days. Conversely, only five (19%) of the 26 patients who did not clear virus are alive; 19 patients died from COVID-19 or related infections, and two died from lymphoma. Unsuccessful virus clearance was significantly associated with age >65 years, use of cytarabine and use of steroid therapy before and during SARS-CoV-2 detection (Table 2).

Intensity and activity of first-line chemotherapy

A total of 43 (67%) of the 64 patients with SARS-CoV-2 infection detected during/before first-line treatment resumed, initiated, or completed anti-lymphoma treatment, with a median (range) delay of 22 (0–116) days. Resumption of anti-lymphoma treatment was strongly conditioned by COVID-19 prognosis (Table 2); it was significantly more common among patients who did not develop pneumonia and patients who cleared the virus. Treatment resumption was more difficult in patients treated with high-dose cytarabine before infection and in patients who received dexamethasone to treat COVID-19 symptoms (Table 2).

Anti-lymphoma treatment was initiated or resumed only after viral clearance in 20 patients and despite persistence of infection in 23, with a median (range) treatment delay of 15 (0–47) and 34 (0–116) days respectively. Initiation/resumption of chemotherapy despite viral persistence was associated with a poorer survival, with a 6-month OS of 70% (95% CI 67%–73%) for the 23 patients who initiated/resumed chemotherapy despite viral persistence and 87% (95% CI 86%–87%) for the 20 patients who initiated/resumed chemotherapy only after virus eradication (p = 0.07). Five of the patients in the first subgroup died from COVID-19 and related infections, whereas none in the second subgroup died from COVID-19. Among used anti-cancer drugs, cytarabine was associated with a higher proportion of treatment interruptions or delays: only six (30%) of the 20 patients who received high-dose cytarabine before virus detection initiated or resumed anti-PCNSL treatment, with a delay of 0–52 days; treatment was not resumed due to COVID-19-related death in the other 11 patients, and consolidative ASCT was delayed in the other three. Conversely, 37 (84%) of the 44 patients who did not receive high-dose cytarabine before virus infection initiated/resumed treatment (Table 2).

Overall, the best lymphoma response achieved in the 64 patients infected before/during first-line treatment was complete in 23 (36%, 95% CI 25%–48%) and partial in 19, with an overall response rate of 66% (95% CI 53%–76%). In all, 10 patients had stable or progressive disease; response was not assessed in 10 patients who died from COVID-19, and treatment was ongoing in two patients.

SARS-CoV-2 infection during next-line/salvage PCNSL treatment

A SARS-CoV-2 infection was diagnosed during salvage anti-lymphoma therapy in six patients; all of them had comorbidities related to greater COVID-19 severity, including a prior cancer in three of them. These patients experienced lymphoma recurrence after a median (range) of 9 (2–30) months since the conclusion of the first-line chemotherapy. The period between lymphoma recurrence and viral infection was ≤2 months in all cases but one. Five patients were hospitalised after SARS-CoV-2 detection, but none was admitted in the ICU; four of them were unable to clear virus, interrupted anti-lymphoma treatment, and three of them died from COVID-19 within 2 weeks. Two patients cleared the virus: one crossed to rituximab-lenalidomide treatment, but died from septic complications after 169 days and the other received whole-brain radiotherapy (WBRT) during infection, achieved a complete remission and was alive at 264 days from infection.

SARS-CoV-2 infection during follow-up in patients without active lymphoma

A SARS-CoV-2 infection was diagnosed during lymphoma follow-up in 21 patients. All these patients had been treated with high-dose methotrexate (HD-MTX)-based chemo-immunotherapy as first-line treatment, followed by consolidation in 15 (Table 1). SARS-CoV-2 infection was diagnosed in first lymphoma remission in 14 patients, in second remission in five and in third remission in two. The median (range) duration of the period between last anti-lymphoma treatment and diagnosis of SARS-CoV-2 was 15 (1–72) months. Eight patients developed pneumonia; the other 13 had mild symptoms, usually with cough and fever. None of the investigated variables (age, gender, comorbidities, and prior treatments) were associated with a higher incidence of pneumonia

TABLE 2 Determining clinical variables in patients infected before or during first-line anti-lymphoma treatment ($n = 64$)

		Pneumonia ($n = 38$)			Hospital discharge ($n = 38$)			Viral clearance ($n = 64$)			Lymphoma treatment resumption ($n = 64$)			
Variable	Subgroups	*N*	Events, *n* (%)	*p*	*N*	Patients alive, *n* (%)	*p*	*N*	Cleared virus, *n* (%)	*p*	*N*	Treatment resumption, *n* (%)	Treatment delay, days, median (range)	*p*
PCNSL therapy	At diagnosis	14	6 (43)	0.15	6	3 (50)	1.00	14	7 (50)	0.54	14	10 (71)	15 (0–46)	0.35
	During 1st-line	50	32 (64)		32	18 (56)		50	31 (62)		50	32 (64)	18 (0–116)	
Risk comorbidities[a]	None	21	14 (67)	0.41	14	8 (57)	0.91	21	14 (67)	0.63	21	14 (67)	21 (0–112)	0.90
	≥1	43	24 (56)		24	13 (54)		43	24 (56)		43	28 (82)	18 (0–116)	
Age, years	≤65	32	20 (63)	0.61	20	12 (60)	0.53	32	23 (72)	0.04	32	22 (69)	15 (0–112)	0.59
	>65	32	18 (56)		18	9 (50)		32	15 (47)		32	20 (63)	21 (0–116)	
Gender	Female	25	16 (64)	0.54	16	10 (63)	0.44	25	14 (56)	0.65	25	16 (64)	23 (0–52)	0.83
	Male	39	22 (56)		22	11 (50)		39	24 (62)		39	26 (67)	15 (0–116)	
Vaccination	No	47	32 (68)	0.02	32	15 (47)	0.049	47	25 (53)	0.35	47	27 (57)	25 (0–116)	0.06
	Yes	14	5 (36)		5	5 (100)		14	10 (71)		14	12 (86)	8 (0–30)	
	unknown	1	1 (–)		1	1 (–)		3	3 (–)		3	3 (–)		
Steroids amount[b], mg	≤100	29	13 (45)	0.04	13	11 (85)	0.01	29	21 (72)	0.14	29	22 (76)	15 (0–112)	0.07
	>100	28	20 (71)		20	8 (40)		28	15 (54)		28	15 (54)	23 (0–116)	
	Undefined	7	5 (–)		5	2 (–)		7	2 (–)		7	5 (–)		
Steroids exposure, weeks	≤2	31	14 (45)	0.03	14	11 (79)	0.03	31	21 (68)	0.43	31	22 (71)	15 (0–112)	0.29
	>2	26	19 (73)		19	8 (42)		26	15 (58)		26	15 (58)	22 (0–116)	
	Undefined	7	5 (–)		5	2 (–)		7	2 (–)		7	5 (–)		
Rituximab[c]	No	16	7 (44)	0.14	7	3 (43)	0.67	16	8 (50)	0.39	16	12 (75)	19 (0–46)	0.54
	Yes	48	31 (65)		31	18 (58)		48	30 (63)		48	30 (63)	19 (0–116)	
HD-cytarabine[c]	No	44	20 (45)	0.0008	20	13 (65)	0.20	44	30 (68)	0.03	44	37 (84)	19 (0–116)	0.00001
	Yes	20	18 (90)		18	8 (44)		20	8 (40)		20	5 (25)	31 (0–52)	
Alkylating agent[c]	No	25	13 (52)	0.33	13	5 (38)	0.31	25	13 (52)	0.43	25	17 (68)	6 (0–46)	0.74
	Yes	39	25 (64)		25	16 (64)		39	25 (64)		39	25 (64)	25 (0–116)	
Pneumonia	No	-	-	-	-	-	-	26	20 (77)	0.01	26	23 (88)	15 (0–88)	0.001
	Yes	-	-		-	-		38	18 (47)		38	19 (50)	26 (0–116)	
Antiviral drugs	No	-	-	-	15	6 (40)	0.18	36	21 (58)	0.33	36	25 (69)	16 (0–112)	0.46
	Yes	-	-		23	15 (65)		28	17 (61)		28	17 (61)	20 (0–116)	
Dexamethasone[d]	No	-	-	-	12	8 (67)	0.48	31	24 (77)	0.004	30	26 (87)	21 (0–80)	0.001
	Yes	-	-		26	13 (50)		33	14 (42)		33	15 (45)	15 (0–116)	
Anticoagulant	No	-	-	-	12	5 (41)	0.20	27	17 (63)	0.81	27	19 (70)	13 (0–80)	0.89
	Yes	-	-		25	16 (64)		35	21 (60)		35	22 (63)	22 (0–116)	
	Unknown	-	-		1	0 (–)								
Viral clearance	No	-	-	-	20	3 (15)	0.00001	-	-	-	26	8 (31)	11 (0–47)	0.00001
	Yes	-	-		18	18 (100)		-	-		38	34 (89)	22 (0–116)	
Pandemic wave[e]	First	24	15 (63)	0.63	15	9 (60)	0.89	24	16 (67)	0.46	24	18 (75)	28 (0–112)	0.04
	Second	16	12 (75)	0.38	12	6 (50)	0.90	16	8 (50)	0.76	16	6 (38)	22 (0–50)	0.99
	Third	24	11 (46)		11	6 (55)		24	14 (58)		24	19 (79)	6 (0–116)	

Abbreviations: HD, high dose; PCNSL, primary central nervous system lymphoma.

[a]This variable regards all comorbidities previously reported as related to higher COVID-19 severity.[17,18] Patients with at least one comorbidity were compared with patients without any comorbidity.

[b]Total amount of steroids received before severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) detection, expressed in milligrammes of dexamethasone.

[c]Drugs received before SARS-CoV-2 detection, regardless of the planned regimen.

[d]Dexamethasone used to treat coronavirus disease 2019 (COVID-19)-related symptoms.

[e]The upper *p* value results from comparison between first and second wave and the lower *p* value results from the comparison between the second and the third wave.

(data not shown). Only patients with pneumonia received specific treatments: varied antiviral agents in five, steroids in three and low-molecular-weight heparin in five. Patients with pneumonia were hospitalised for a median (range) of 9 (4–25) days; only one of them was admitted to the ICU for 4 days, requiring non-invasive ventilation. All the 21 patients cleared the virus, with a median (range) time to viral clearance of 22 (2–226) days. At a median (range) follow-up from diagnosis of SARS-CoV-2 infection of 213 (25–461) days, 20 (95%) patients are alive; the only death occurred in a patient who experienced lymphoma recurrence after 1 month from SARS-CoV-2 infection and had fatal intestinal perforation during salvage chemotherapy.

Survival and post-COVID-19 assessments on the whole series

At a median (range) follow-up since virus detection of 185 (18–534) days, 59 (65%) patients are alive, 34 (37%)

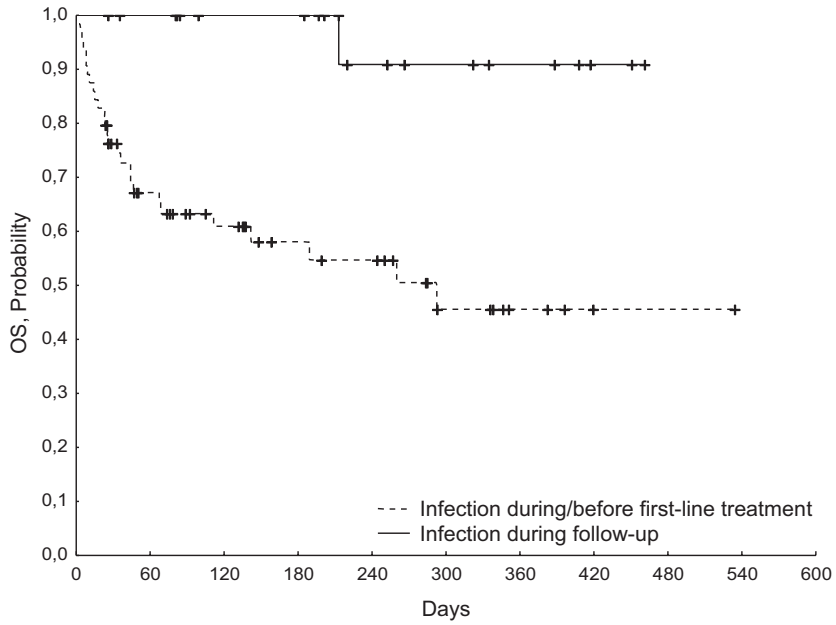

FIGURE 2 Overall survival (OS) curves of patients divided according to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) diagnosis and anti-lymphoma treatment. The 6-month overall survival was 58% (95% confidence interval [CI] 54%–62%) for the 64 patients with SARS-CoV-2 infection diagnosed immediately before or during first-line anti-PCNSL treatment (dotted line) and 100% (95% CI 100%–100%) for the 21 patients with SARS-CoV-2 infection diagnosed during follow-up (continued line) ($p = 0.0005$).

without evidence of lymphoma. A total of 32 patients died: the cause was COVID-19 in 19 (21%) patients, other infections (*Acinetobacter*, *Enterococcus faecium*, aspergillosis) in five, post-COVID-19 sequelae in one, chemotherapy complications in two, and lymphoma in five. The 1-, 6- and 12-month OS was 80% (95% CI 79%–81%), 66% (95% CI 64%–68%) and 55% (95% CI = 50%–60%) respectively.

During the period of analysis, 20 (22%) patients had lymphoma progression or relapse after recovery from COVID-19, with a 12-month event-free survival of 43% (95% CI 33%–52%). The 21 patients with SARS-CoV-2 infection diagnosed during follow-up showed a significantly better OS than the 64 patients with SARS-CoV-2 infection diagnosed immediately before or during first-line anti-PCNSL treatment (6-month OS: 100% and 58%, $p = 0.0005$) (Figure 2). Multivariable analysis confirmed that virus persistence and pre-COVID-19 steroid therapy were independently associated with poor OS (Table 3).

This study did not show a significant association between comorbidities and COVID-19-related mortality, with rates of 29% (10/34) for patients with high blood pressure, 42% (10/24) for patients with history of vasculopathy/coronaropathy/cardiopathy, 30% (three of 10) for patients with hypercholesterolaemia, 25% (three of 12) for patients with obesity/overweight, and 55% (six of 11) for diabetic patients; none of these rates was significantly different than the 25% (six of 24) recorded in patients with no comorbidities, with p values of 0.76, 0.35, 0.99, 0.99 and 0.12 respectively. COVID-19-related mortality was 43% in patients with two or more of these comorbidities (10/23, $p = 0.22$). When analysis was limited to patients infected before/during first-line treatment (Table 2), comorbidities were not associated with risk of pneumoniae, viral clearance, treatment delay, or COVID-19-related mortality.

Overall, 61 (67%) patients cleared the virus. SARS-CoV-2 reinfection was diagnosed in nine patients at a median (range) of 61 (10–452) days from initial viral clearance; two of these patients were previously vaccinated. Seven of the nine patients had reinfection during first-line treatment (Figure 1) and two during follow-up. Three patients died from COVID-19 after reinfection.

At a median (range) of 338 (30–403) days after virus detection, 18 patients received at least a dose of anti-COVID-19 vaccine. SARS-CoV-2 serology was assessed at the last control visit in 30 (18 vaccinated and 12 unvaccinated) patients at a median (range) time from virus detection of 10 (1–224) days; seroconversion was demonstrated in 11 (61%) and six (50%) patients, respectively.

Pandemic wave, virus variants, vaccination, and geographical discrepancies

Mortality during the three considered waves was not significantly different (Table 4), with a 6-month OS of 76% (95% CI 75%–77%), 50% (95% CI 39%–60%) and 52% (95% CI 38%–64%) respectively ($p = 0.27$). Importantly, mortality in the third wave was significantly different between vaccinated ($n = 16$) and unvaccinated ($n = 17$) patients: all the 16 vaccinated patients cleared the virus, continued chemotherapy and survived SARS-CoV-2 infection, whereas nine of the 17 unvaccinated patients cleared the virus and eight survived virus infection ($p = 0.0009$). The 6-month OS was 86% in

TABLE 3 Multivariable analysis

Variable	Subgroups	*N*	HR (95% CI)	*p*
Treatment	Follow-up First line	21 64	0.50 (0.05–4.80)	0.55
Age, years	≤65 >65	44 41	1.23 (0.50–3.04)	0.64
Steroids amount, mg	≤100 >100	46 29	7.50 (1.78–31.6)	0.006
Steroids exposure, weeks	≤2 >2	50 27	0.27 (0.06–1.14)	0.07
Cytarabine[a]	No Yes	44 20	0.61 (0.25–1.46)	0.27
Pneumonia	No Yes	39 46	1.63 (0.56–4.70)	0.36
Dexamethasone[b]	No Yes	48 36	1.23 (0.44–3.46)	0.68
Viral clearance	No Yes	26 59	0.03 (0.00–0.10)	0.00001

Note: Patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection during salvage therapy were excluded.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Drug received before SARS-CoV-2 detection, regardless of the planned regimen.

[b]Delivered to treat coronavirus disease 2019-related inflammation.

TABLE 4 Outcome according to pandemic wave and geographical regions

Country	1st wave, *n* (%)	2nd wave, *n* (%)	3rd wave, *n* (%)	Total, *n*	Mortality rate, *n* (%)	Follow-up, days, median	6-month OS, %	Vaccinated patients[a], *n* (%)
France	15 (43)	3 (9)	17 (49)	35	5 (14)	135	86	11 (31)
Italy	11 (38)	9 (31)	9 (31)	29	15 (52)	148	51	3 (10)
UK	5 (36)	5 (36)	4 (29)	14	7 (50)	256	50	0 (0)
USA	6 (50)	3 (25)	3 (25)	12	4 (33)	212	71	2 (17)
Total	37 (41)	20 (22)	33 (37)	90	31 (34)	185	66	16 (18)
Mortality	12 (32)	10 (50)	9 (27)	31				
Follow-up, days, median	334	200	50					
6-month OS, %	76	50	52					

Note: One patient from Israel was excluded.

Abbreviation: OS, overall survival.

[a]Percentage on the total number of patients per country.

France, 51% in Italy, 50% in UK and 71% in USA (Table 4). However, this difference seems to be associated with a larger prevalence of patients from the third wave and, consequently, of vaccinated patients.

Although information on virus variant was fragmentary, the 16 patients diagnosed after November 2021, the date when Omicron became the variant of concern according to the WHO, merit mentioning. In all, 14 of these patients were vaccinated before SARS-CoV-2 infection. Although the follow-up of these patients was shorter than 3 months (range 25–93 days), overall outcome appears favourable: there were only two deaths from COVID-19, which occurred in the two unvaccinated patients, whereas all vaccinated patients are alive and resumed/completed chemotherapy with a median (range) delay of 3 (0–28) days.

DISCUSSION

To the best of our knowledge, this is the largest study focused on consecutive patients with PCNSL and concurrent SARS-CoV-2 infection. Overall, results of this international study performed at 27 centres in five countries, were encouraging: two-thirds of the whole analysed series were alive at 6 months, with PCNSL remission in most of them. Half of patients infected during first-line chemotherapy cleared the virus, even in subjects with pneumonia. The latter complication was more common among patients who received steroids at high doses or for >2 weeks before virus detection. Two-thirds of patients initiated, resumed, or completed first-line treatment, with an acceptable delay. Treatment resumption was more common among patients who did not

develop pneumonia, cleared the virus, or did not receive steroids during infection. The present data suggests that delaying chemotherapy until virus eradication can be a safe option, particularly when high-dose cytarabine is being used and patients received high dose of steroids before infection. Prevention of pneumonia and rapid virus eradication are the main goals to favour timely treatment resumption, maintaining cure as the primary objective in these high-risk patients. Importantly, SARS-CoV-2 infection in patients with PCNSL in follow-up was associated with mild symptoms and a high virus clearance rate, whereas the risk of mortality was higher in patients undergoing salvage treatment.

This study has some limitations. First, retrospective data collection may result in some selection and interpretation bias. Although the low incidence of PCNSL allowed participating researchers to collect data from all the consecutive patients seen at each institution, we cannot exclude a favourable selection bias due to the fact that infected patients with very poor conditions were not reported to the haematologist. Second, due to absence of a defined standard therapy and several changes in anti-COVID-19 guidelines, various therapeutic approaches were used, hindering the ability to draw reliable recommendations on optimal COVID-19 therapy in this setting. However, data analysed allowed us to identify patient- and treatment-related risk factors and to provide some suggestions on PCNSL treatment that could contribute to reduce mortality. Third, alternative modalities to confirm viral clearance were carried out among involved centres. Of note, the nasal swab after the quarantine period and/or at resolution of the symptoms was not applied in all centres, introducing inevitable bias, and a probable overestimation of the time to viral clearance in patients infected during lymphoma follow-up. Although this should not interfere with conclusions on the management of patients during first-line treatment, which constitutes the most important finding of this study, the present results on viral clearance should be applied with caution in clinical practice. Fourth, the restricted information regarding the variants of the virus that affected the analysed population did not allow us to analyse this data as a statistical variant; only cases diagnosed after November 2021, when the Omicron variant became prevalent in countries where study was conducted, were analysed separately. Fifth, the small number of patients who received COVID-19 vaccine does not allow us to draw reliable conclusions on this protective strategy. Nevertheless, our results seem to suggest a benefit of vaccination on pneumonia incidence, COVID-19-related mortality and lymphoma treatment resumption. Importantly, overall conclusions of the present series, largely collected in the pre-vaccine era, seem applicable also in the vaccination era as recent studies suggest that the risk of severe COVID-19 remains high after full vaccination in patients with cancer.[23–25] However, there are no clear data demonstrating that impaired antibody response is associated with severe COVID-19 in patients with haematological tumours as the small number of vaccinated patients affected by these neoplasms in published studies.

Type, severity, and frequency of COVID-19 presenting symptoms in the present study were similar to those previously reported in pre-vaccine series of solid and haematological tumours.[6,26–30] An important issue that characterises the management of patients with PCNSL is the wide use of steroids to control symptoms related to the expansive brain mass and concomitant oedema, particularly in the weeks before diagnosis and during the first weeks of chemotherapy. The present study suggests that the use of steroids for >2 weeks was associated with a significantly higher incidence of COVID-19 pneumonia, which negatively affected the overall outcome. Noteworthy, all the patients who received steroids for ≥1 month before viral detection developed pneumonia, and two-thirds of them died early from COVID-19 or related complications, which is in line with the high COVID-19 mortality recorded among patients with rheumatic disease treated with steroid therapy.[31] Accordingly, avoiding or minimising the use of steroids as soon as possible, performing an early diagnostic biopsy and starting timely chemotherapy, is an advisable strategy, even more during the SARS-CoV-2 pandemic.

Overall mortality in the present whole series was 35%, with a 6-month OS of 66%. Although the present results are similar to those reported in other studies on patients with lymphoma,[5,26] it is our opinion that these survival figures are encouraging for PCNSL, a neoplasm requiring an intensive treatment and with a substantially poorer prognosis compared to many other lymphomas. Mortality was different in the three considered subgroups. Despite patients infected during follow-up (i.e., lymphoma remission) had received full doses of one or more treatment lines and anti-CD20 therapy, SARS-CoV-2 infection was associated with mild symptoms, and no patient died from COVID-19. This could be explained at least in part by the fact that these patients did not receive steroids for months before virus infection, which is confirmed by multivariable analysis (Table 3). The good prognosis of these patients suggests that they can be managed safely, with less hospitalisation requirements, and following recommendations for infected subjects of the general population. Conversely, mortality was high in the small subgroup of patients infected during salvage therapy, which may be explained by the profound myelotoxicity of different lines of treatment, use of high doses of steroids, and high-risk comorbidity. Outcome in patients infected before/during the first-line chemotherapy was promising in terms of the high virus eradication rate and acceptable anti-lymphoma treatment delay (median ~1 month). In contrast to prior studies suggesting an improved survival in the second or further pandemic waves,[6] our analysis did not show a difference in COVID-19 severity, viral clearance, chemotherapy resumption, and survival among the analysed waves. This may be explained by a higher proportion of asymptomatic patients and more diffuse use of effective antiviral treatments in the more recent waves in prior studies,[6] whereas only a few patients in the present study received monoclonal antibodies, antiviral drugs or convalescent plasma.

The presence of active, residual tumour seems to be associated with a higher COVID-19 mortality in onco-haematological patients, but available literature is controversial.[26,32] However, this unfavourable prognostic effect seems to be confirmed by the above-mentioned excellent prognosis of patients infected during lymphoma remission. When SARS-CoV-2 is detected in patients with PCNSL at diagnosis or during initial chemotherapy, we should make every effort to achieve and maintain a rapid complete tumour remission. Thus, starting an effective antiviral therapy early, with novel monoclonal antibodies and other antiviral agents, seems advisable as viral clearance is strongly associated with survival, and contributes to maintaining chemotherapy dose intensity.[33,34] The latter is an important issue considering that chemotherapy administration during infection persistence was associated with an increased risk of mortality, especially when high-dose cytarabine-containing combinations were used. This may be explained in part by the high COVID-19 mortality rates reported in patients with lymphoma treated with anti-cancer drugs associated with severe haematological toxicity.[28,35,36]

In conclusion, accurate SARS-CoV-2 monitoring, vaccination, early antiviral treatment, delay of cytarabine, and, when clinically possible, avoidance of dexamethasone use during infection result in promising outcome in this high-risk setting. Avoiding prolonged steroid therapy could result in lower incidence of pneumonia and hospitalisation, and a diffuse and timely use of effective antiviral agents could lead to earlier viral clearance, preserving chemotherapy dose intensity and thereby improving survival. When possible, chemotherapy should be indicated or resumed after viral clearance, with treatment de-escalation in case of prolonged virus persistence, especially in unvaccinated patients. Patients infected during lymphoma remission had mild symptoms, with less frequent hospitalisations and lower mortality, requiring similar measures as infected subjects in the general population. Notably, the low seroconversion rates both in vaccinated and unvaccinated patients remain a major concern.

AUTHOR CONTRIBUTIONS

Sara Steffanoni, Teresa Calimeri, Andrés J. M. Ferreri and Kate Cwynarski designed the research study. Sara Steffanoni, Teresa Calimeri, Alice Laurenge, Christopher P. Fox, Carole Soussain, Christian Grommes, Maria Chiara Tisi, Jesca Boot, Nicola Crosbie, Carlo Visco, Luca Arcaini, Sridhar Chaganti, Marianna C. Sassone, Alvaro Alencar, Daniele Armiento, Ilaria Romano, Jorg Dietrich, Gilad Itchaki, Riccardo Bruna, Nicola S. Fracchiolla, Laura Arletti, Adriano Venditti, Stephen Booth, Pellegrino Musto and Khê Hoang Xuan collected patient data; Tracy T. Batchelor contributed essential tools; Sara Steffanoni, Teresa Calimeri and Andrés J. M. Ferreri analysed the data, Sara Steffanoni, Teresa Calimeri, Kate Cwynarski and Andrés J. M. Ferreri wrote the paper; all authors approved the final manuscript and submission.

ACKNOWLEDGEMENT

Open access funding provided by BIBLIOSAN.

CONFLICT OF INTEREST

No conflicts of interest are disclosed.

ORCID

Christopher P. Fox https://orcid.org/0000-0002-6322-9254
Gilad Itchaki https://orcid.org/0000-0002-9064-8139
Adriano Venditti https://orcid.org/0000-0002-0245-0553
Stephen Booth https://orcid.org/0000-0003-2687-0234
Andrés J. M. Ferreri https://orcid.org/0000-0001-9606-6124

REFERENCES

1. de Azambuja E, Brandao M, Wildiers H, Laenen A, Aspeslagh S, Fontaine C, et al. Impact of solid cancer on in-hospital mortality overall and among different subgroups of patients with COVID-19: a nationwide, population-based analysis. ESMO Open. 2020;5(5):e000947-000947.
2. Vuagnat P, Frelaut M, Ramtohul T, Basse C, Diakite S, Noret A, et al. COVID-19 in breast cancer patients: a cohort at the Institut curie hospitals in the Paris area. Breast Cancer Res. 2020;22(1):55–020–01293-8.
3. Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet. 2020;395(10241):1907–18.
4. Zarifkar P, Kamath A, Robinson C, Morgulchik N, Shah SFH, Cheng TKM, et al. Clinical characteristics and outcomes in patients with COVID-19 and cancer: a systematic review and meta-analysis. Clin Oncol (R Coll Radiol). 2021;33(3):e180–91.
5. Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. Lancet Haematol. 2020;7(10):e737–45.
6. Pagano L, Salmanton-Garcia J, Marchesi F, Busca A, Corradini P, Hoenigl M, et al. COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association survey (EPICOVIDEHA). J Hematol Oncol. 2021;14(1):168–021–01177-0.
7. Perini GF, Fischer T, Gaiolla RD, Rocha TB, Bellesso M, Teixeira LLC, et al. How to manage lymphoid malignancies during novel 2019 coronavirus (CoVid-19) outbreak: a Brazilian task force recommendation. Hematol Transfus Cell Ther. 2020;42(2):103–10.
8. Di Ciaccio P, McCaughan G, Trotman J, Ho PJ, Cheah CY, Gangatharan S, et al. Australian and New Zealand consensus statement on the management of lymphoma, chronic lymphocytic leukaemia and myeloma during the COVID-19 pandemic. Intern Med J. 2020;50(6):667–79.
9. Waghmare A, Abidi MZ, Boeckh M, Chemaly RF, Dadwal S, El Boghdadly Z, et al. Guidelines for COVID-19 Management in Hematopoietic Cell Transplantation and Cellular Therapy Recipients. Biol Blood Marrow Transplant. 2020;26(11):1983–94.
10. Willan J, King AJ, Hayes S, Collins GP, Peniket A. Care of haematology patients in a COVID-19 epidemic. Br J Haematol. 2020;189(2):241–3.
11. Weinkove R, McQuilten ZK, Adler J, Agar MR, Blyth E, Cheng AC, et al. Managing haematology and oncology patients during the COVID-19 pandemic: interim consensus guidance. Med J Aust. 2020;212(10):481–9.
12. Rasschaert M, Vanclooster P, Depauw L, Mertens T, Roelant E, Coenen E, et al. Meeting the challenges in cancer care management during the SARS-Cov-2 pandemic: a retrospective analysis. Cancer Control. 2021;28:1–9.
13. Ribera JM, Morgades M, Coll R, Barba P, Lopez-Lorenzo JL, Montesinos P, et al. Frequency, clinical characteristics and outcome of adults with acute lymphoblastic leukemia and COVID 19 infection

in the first vs. Second Pandemic Wave in Spain. Clin Lymphoma Myeloma Leuk. 2021;21(10):e801–9.
14. Sanchez-Velazquez A, Bauer-Alonso A, Estrach T, Vega-Diez D, Garcia-Muret P, Haya L, et al. Patients with primary cutaneous lymphoma are at risk for severe COVID-19. Data from the Spanish primary cutaneous lymphoma registry. J Eur Acad Dermatol Venereol. 2021;35(10):e624–6.
15. Chatzikonstantinou T, Kapetanakis A, Scarfo L, Karakatsoulis G, Allsup D, Cabrero AA, et al. COVID-19 severity and mortality in patients with CLL: an update of the international ERIC and campus CLL study. Leukemia. 2021;35(12):3444–54.
16. Laurenge A, Ursu R, Houillier C, Abdi B, Tebano G, Quemeneur C, et al. SARS-CoV-2 infection in patients with primary central nervous system lymphoma. J Neurol. 2021;268(9):3072–80.
17. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med. 2020;25:1–8.
18. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. JAMA Intern Med. 2020;180(8):1081–9.
19. Abrey LE, Batchelor TT, Ferreri AJ, Gospodarowicz M, Pulczynski EJ, Zucca E, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol. 2005;23(22):5034–43.
20. Abrey LE, Yahalom J, DeAngelis LM. Treatment for primary CNS lymphoma: the next step. J Clin Oncol. 2000;18(17):3144–50.
21. Fritsch K, Kasenda B, Schorb E, Hau P, Bloehdorn J, Mohle R, et al. High-dose methotrexate-based immuno-chemotherapy for elderly primary CNS lymphoma patients (PRIMAIN study). Leukemia. 2017;31(4):846–52.
22. Ferreri AJ, Cwynarski K, Pulczynski E, Ponzoni M, Deckert M, Politi LS, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the international Extranodal lymphoma study Group-32 (IELSG32) phase 2 trial. Lancet Haematol. 2016;3(5):e217–27.
23. Herishanu Y, Rahav G, Levi S, Braester A, Itchaki G, Bairey O, et al. Efficacy of a third BNT162b2 mRNA COVID-19 vaccine dose in patients with CLL who failed standard two-dose vaccination. Blood. 2022;139(5):678–85.
24. Perry C, Luttwak E, Balaban R, Shefer G, Morales MM, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-Hodgkin lymphoma. Blood Adv. 2021;5(16):3053–61.
25. Schmidt AL, Labaki C, Hsu CY, Bakouny Z, Balanchivadze N, Berg SA, et al. COVID-19 vaccination and breakthrough infections in patients with cancer. Ann Oncol. 2022;33(3):340–6.
26. Regalado-Artamendi I, Jimenez-Ubieto A, Hernandez-Rivas JA, Navarro B, Nunez L, Alaez C, et al. Risk factors and mortality of COVID-19 in patients with lymphoma: a multicenter study. Hema. 2021;5(3):e538.
27. Robilotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med. 2020;26(8):1218–23.
28. Lamure S, Dulery R, Di Blasi R, Chauchet A, Laureana C, Deau-Fischer B, et al. Determinants of outcome in Covid-19 hospitalized patients with lymphoma: a retrospective multicentric cohort study. EClinicalMedicine. 2020;27:100549.
29. Mato AR, Roeker LE, Lamanna N, Allan JN, Leslie L, Pagel JM, et al. Outcomes of COVID-19 in patients with CLL: a multicenter international experience. Blood. 2020;136(10):1134–43.
30. Sah P, Fitzpatrick MC, Zimmer CF, Abdollahi E, Juden-Kelly L, Moghadas SM, et al. Asymptomatic SARS-CoV-2 infection: a systematic review and meta-analysis. Proc Natl Acad Sci U S A. 2021;118(34):1–12.
31. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 global rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2020;79(7):859–66.
32. Vijenthira A, Gong I, Betschel SD, Cheung M, Hicks LK. Vaccine response following anti-CD20 therapy: a systematic review and meta-analysis of 905 patients. Blood Adv. 2021;5(12):2624–43.
33. Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early Remdesivir to prevent progression to severe Covid-19 in outpatients. N Engl J Med. 2022;386(4):305–15.
34. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for Oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med. 2022;386(6):509–20.
35. Gafter-Gvili A, Polliack A. Bendamustine associated immune suppression and infections during therapy of hematological malignancies. Leuk Lymphoma. 2016;57(3):512–9.
36. Visco C, Marcheselli L, Mina R, Sassone M, Guidetti A, Penna D, et al. A prognostic model for patients with lymphoma and COVID-19: a multicentre cohort study. Blood Adv. 2022;6(1):327–38.

How to cite this article: Steffanoni S, Calimeri T, Laurenge A, Fox CP, Soussain C & Grommes C et al. Impact of severe acute respiratory syndrome coronavirus-2 infection on the outcome of primary central nervous system lymphoma treatment: A study of the International PCNSL Collaborative Group. Br J Haematol. 2022;00:1–13. https://doi.org/10.1111/bjh.18396