bjh short report

Managing the front-line treatment for diffuse large B cell lymphoma and high-grade B cell lymphoma during the COVID-19 outbreak

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Summary

The COVID-19 pandemic has dramatically challenged care for cancer patients, especially those with active treatment who represent a vulnerable population for SARS-CoV-2 infection. Aggressive lymphoid neoplasms, such as diffuse large B cell lymphoma and high-grade B cell lymphoma, need to be treated without delay in order to get the best disease outcome. Because of that, our clinical practice was changed to minimise the risk of SARS-CoV-2 infection while continuing haematological treatment. In this report, we analyse the management of front-line therapy in 18 patients during the COVID-19 outbreak, as well as the results of the implemented measures in their outcome.

Keywords: B cell lymphoma, COVID-19, high-grade, haematological malignancies, SARS-CoV-2.

The COVID-19 pandemic has dramatically challenged care for cancer patients. Among them, those with haematological malignancies, particularly lymphoid neoplasms, represent one of the most vulnerable populations. In addition to the immune deregulation caused by lymphoma, many patients receive therapy that causes profound immune suppression. At the beginning of the current outbreak, our main worries were the implications of treatment delay on outcomes in this population, the risks of continuing treatment, how to protect our patients, the threat of infection among these patients and, lastly, how long the outbreak of COVID-19 would last.

At the beginning, few guidelines regarding the management of lymphoid malignancies during COVID-19 pandemic were available.[1,2] As treatment of patients with diffuse large B cell lymphoma (DLBCL) and high-grade B cell lymphoma (HGBL) cannot be delayed without detrimental effects on the outcomes, we had to adapt our clinical practices to cope with these concerns. We have conducted an analysis on the effect of COVID-19 pandemic in the front-line therapy of patients with DLBCL and HGBL.

Material and methods

All patients who were receiving front-line treatment for DLBCL and HGBL at La Paz University Hospital from March 1 to May 31, 2020, were included in this analysis. Patients under salvage therapy or in follow-up after the end of treatment were not included.

Due to epidemiological context, several specific measures were adopted in order to minimise risk of SARS-CoV-2 infection in these patients as well as to guarantee the continuation of their therapy. In order to keep our installations as a COVID-19-free area, a checklist of symptoms and temperature screening was done before accessing the outpatient area for patients who should be necessarily attended. No entry was allowed for any individual with suspicion of COVID-19, and no visitors (i.e., family, companions) were permitted. Follow-up was done remotely by telemedicine for patients who were not receiving active treatment, if possible.

Immune-chemotherapy treatments were not postponed exclusively because of pandemic context in any patient. As a

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protective measure, patients were tested for SARS-CoV-2 by nasopharyngeal swab before each new treatment.

R-CHOP was the chosen treatment for patients with DLBCL, administered as an outpatient regimen. HGBL patients were treated with intensive therapy such as dose-adjusted EPOCH-(R) (DA-EPOCH-R), which require hospitalisation. Elderly patients received attenuated regimens (R-mini-CHOP).

Primary prophylaxis with G-CSF was taken by most of the patients as a way of preventing neutropenia.

Results

A total of 18 patients with DLBCL and HGBL were attended during the period of time of the study in our hospital, including seven women and 11 men. The median age was 57 years (range 27–82). The clinical and demographic characteristics of these patients are summarised in Table I.

Only three patients had a different diagnosis from DLBCL: one was diagnosed with plasmablastic lymphoma, while the other two had HGBL not otherwise specified (NOS). Among the patients with DLBCL diagnosis, one of them was transformed from a splenic marginal zone lymphoma.

Regarding treatment, three patients received DA-EPOCH (only one of them combined with rituximab due to plasmablastic origin in patient 2 and lack of CD20 expression in patient 3), 11 were treated with R-CHOP (combined with bispecific CD3/CD20 monoclonal antibody in one patient under clinical trial) and four received R-mini-CHOP because of their age.

Primary prophylaxis with G-CSF was administered in seven patients from days 8–10 of cycle for 3–5 days. Five of them started first cycle of chemotherapy after the lockdown. If chemotherapy had already been administered before COVID-19 outbreak, prophylactic G-CSF was only provided to patients who had developed neutropenia before (secondary prophylaxis). Patients in treatment with DA-EPOCH regimen also received prophylactic G-CSF as it is part of the protocol.

Neutropenic fever was only observed in patient 10, on day 10 of first cycle of chemotherapy, while she was receiving G-CSF. Although our patient did not identify any other symptoms apart from fever, several microbiological tests (including blood stream cultures, urine culture and SARS-CoV-2 PCR) were done. COVID-19 was diagnosed at that moment and treatment with hydroxychloroquine and azithromycin was initiated. Because of the viral diagnosis, thoracic CT was performed, showing bilateral ground-glass opacities and two consolidations suggestive of viral disease. Antibiotic treatment with amoxicillin-clavulanic acid was added, requiring an escalation strategy because of fever persistence, sequentially to levofloxacin, cefepime and, finally, to meropenem and linezolid, reaching fever defervescence. Patient had stable haemodynamic situation without oxygen therapy requirement. Table II shows analytical evolution since administration of the first cycle of treatment and during SARS-COV-2 infection until recovery. Severe neutropenia (grade 4) and lymphopenia (grade 4) were present at the moment of COVID diagnosis, with a progressive increase in the following days after administration of G-CSF from day +10 to +16 and from day +24 to +26. C-reactive protein was also monitored, reaching a peak value on day +14. Procalcitonin was slightly elevated on day +18, showing a probable bacterial superinfection. No other microbiological isolation was detected. Second chemotherapy cycle had to be postponed 8 days until resolution of infection, confirmed by two consecutively-negative SARS-CoV-2 PCR prior to treatment administration.

We did not register any other febrile neutropenia in our cohort.

As lymphopenia has been described as a common finding during SARS-CoV-2 infection, we analysed minimum lymphocyte count among our patients during the time of study. Lymphopenia (defined as $<1.1 \times 10^9$ lymphocytes/l) was observed in 16 patients. A minimum of $0{\cdot}05 \times 10^9$ lymphocytes/l was detected in patient 10, simultaneous with COVID-19 diagnosis, as shown in Table II. Among patients without lymphopenia, 50% of them were treated with R-mini-CHOP.

Discussion

In the last 3 months, our hospital has dramatically suffered the impact of the COVID-19 outbreak. In this scenario, our goal was to achieve a balance between risk and benefit for the patients with lymphoid malignancies, one of the most vulnerable populations for SARS-CoV-2 infection. Shah *et al.*[6] has recently described the incidence of lymphoid malignancies among patients with haematological diseases and COVID-19. In their cohort, 77% of infected patients were diagnosed with lymphoid malignancy or plasma cell dyscrasia, a similar proportion to our centre. Because of that, and especially considering patients with aggressive disease, which requires early treatment, our clinical practice was redesigned to optimise benefit while minimising toxicity, viral exposure risk and resource utilisation.[3–5]

R-CHOP continues to be the standard of care for young DLBCL patients, while R-mini-CHOP with growth factor support is the recommended strategy for older and unfit patients. Avoidance of intensified regimens during COVID-19 outbreak, such as DA-EPOCH-R, usually administered in HGBL, has been recommended in recent guidelines[1,2] in order to reduce immunosuppression and potential complications. In contrast, our centre decided to keep these regimens, giving priority to reaching the best disease control and outcome. The measurements implemented to prevent COVID-19 were effective to allow continuing treatment. It should be noted that, unlike a recent publication that describes intensive active treatment as a risk factor for infection,[6] only one of our patients developed mild COVID-19 while receiving

Table I. Clinical and demographic characteristics of patients receiving front-line therapy for DLBCL or HGBL.

	Age	Gender	Comorbidities	Type of lymphoma	Chemotherapy	Disease state	Confirmed SARS-CoV-2 infection	Neutropenic fever	Lower baseline lymphocyte count ($\times 10^9$/l)
Patient 1	27	Male	None	HGBL, NOS	DA-EPOCH-R	Active treatment	No	No	400
Patient 2	57	Male	Type 1 diabetes, HIV, chronic HCV (without active infection), drug user	Plasmablastic lymphoma	DA-EPOCH	Active treatment	No	No	330
Patient 3	57	Female	None	HGBL, NOS	DA-EPOCH	Active treatment	No	No	100
Patient 4	45	Male	HCV infection (active treatment), past HBV infection, drug user	DLBCL	R-CHOP	Active treatment	No	No	1570
Patient 5	49	Male	Past TB infection	DLBCL	R-CHOP	CR	No	No	360
Patient 6	66	Male	None	DLBCL	R-CHOP+ bispecific CD3/CD20 monoclonal antibody	CR	No	No	710
Patient 7	51	Female	Idiopathic cardiomyopathy, primary biliary cholangitis, eating disorder	DLBCL	R-CHOP (with liposomal doxorubicin)	Active treatment	No	No	280
Patient 8	53	Female	Hypertension, hypothyroidism, obesity	DLBCL	R-CHOP	Progression	No	No	480
Patient 9	54	Male	Dyslipidemia	DLBCL	R-CHOP	PR	No	No	410
Patient 10	52	Female	Dyslipidemia	DLBCL	R-CHOP	Active treatment	Yes	Yes	50
Patient 11	63	Male	Prostatic adenocarcinoma (in CR)	DLBCL	R-CHOP	Active treatment	No	No	1350
Patient 12	38	Male	Dyslipidemia	DLBCL	R-CHOP	Active treatment	No	No	1020
Patient 13	70	Male	None	DLBCL	R-CHOP	Active treatment	No	No	1080
Patient 14	70	Male	Hypertension, Type 2 diabetes, Dyslipidemia, Sleep apnoea syndrome, Prostatic adenocarcinoma (with active hormone therapy)	DLBCL	R-CHOP	Active treatment	No	No	400
Patient 15	79	Male	TIA, bradyarrhythmia, Parkinson disease, depressive disorder	DLBCL	R-mini-CHOP	Active treatment	No	No	460
Patient 16	78	Female	Ischemic heart disease, Breast cancer (in CR)	DLBCL	R-mini-CHOP	CR	No	No	1210
Patient 17	80	Female	Hypertension, Type 2 diabetes	DLBCL	R-mini-CHOP	Active treatment	No	No	1250
Patient 18	82	Female	Hypertension, Hypothyroidism	DLBCL transformed from splenic marginal zone lymphoma	R-mini-CHOP	Active treatment	No	No	370

NOS, not otherwise specified; HCV, hepatitis C virus; TB, tuberculosis; TIA, transient ischemic attack; CR, complete remission; PR, partial response.

Table II. Analytical evolution of patient 10 since the first cycle of R-CHOP to administration of second cycle of R-CHOP.

	Day +1 (1st R-CHOP)	Day +10 (COVID diagnosis)	Day +14	Day +18	Day +24	Day +26	Day +30 (2nd R-CHOP)
White blood cell count ($\times 10^9$/l)	2·64	0·11	3	8·25	1·46	17·41	3·31
Neutrophil count ($\times 10^9$/l)	1·69	0·04	2·96	7·86	1·14	16·61	2·48
Lymphocyte count ($\times 10^9$/l)	0·75	0·05	0·12	0·12	0·18	0·26	0·38
Haemoglobin (g/dl)	8·2	12·3	11·1	9·7	10·2	9·6	9·7
Platelets ($\times 10^9$/l)	197	78	121	184	358	402	451
D-dimer (ng/ml)			610	280			
C-reactive protein (mg/l)	21·1	33·5	80·6	47·7	35·3	24·6	6·2
Procalcitonin (ng/ml)			0·51	0·55	0·12		
Lactate dehydrogenase (UI/l)	456	217	235	253	281	240	230
Ferritin (ng/ml)			975	1166	1640		1488

front-line therapy. No patients undergoing intensified treatments were infected by SARS-CoV-2. Likewise, Robilotti *et al.*[7] have recently stated that active chemotherapy in the 30 days prior to COVID-19 does not confer any risk for disease severity, although they show a 12% mortality among cancer patients because of SARS-CoV-2 infection, lower than what has been previously published. Our study results suggest that, despite maintaining aggressive treatments, it is possible to keep our patients free of COVID-19. However, further studies are needed to clarify the importance of prior or active chemotherapy in COVID-19 evolution.

Lymphopenia is a common finding, not only in patients with lymphoma but also in infection by SARS-CoV-2, with a predisposing role to severe viral infection,[8,9] although its definite paper has not been established and some new investigations show a probable association between lymphopenia and better outcome.[6] It is noteworthy that minimum lymphocyte count was registered in our cohort in the only patient who was infected by SARS-CoV-2, simultaneous with the moment of COVID-19 diagnosis. Despite the probable relationship between grade of lymphopenia and severity of COVID-19, our patient presented a favourable evolution. So far, no investigation has been done analysing the importance of lymphopenia as a predictive factor of severe SARS-CoV-2 infection in patients with previous lymphopenia.

It is remarkable that only one infectious event appeared during the study period in our series, which means a very low incidence of febrile neutropenia. No patient required inpatient management, except the one with COVID-19, allowing for limited visits to the hospital. Following international recommendations that advocate for the use of prophylactic G-CSF to minimise the risk of febrile neutropenia, we started this practice in the majority of patients. Although these recommendations had only empiric support, they may have influenced the low incidence of COVID-19 in our cohort.

While new studies are needed to clarify the behaviour of COVID-19 among patients with lymphoid malignancies, we can conclude that successful front-line therapy is possible in these patients during a pandemic outbreak. These results may be owing to a mixture of hygiene measurements, prophylactic actions and clinician and patient awareness. As new SARS-CoV-2 outbreaks are expected, it is important to examine outcomes and learn from these efforts in order to guide health professionals and contribute to future progress.

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