ORIGINAL ARTICLE

Current outcomes of SARS-CoV-2 Omicron variant infection in high-risk hematologic patients early treated with antivirals.

Tommaso-Francesco AIELLO[1*], Pedro PUERTA-ALCALDE[1], Mariana CHUMBITA[1], Carlos LOPERA[1], Patricia MONZÓ[1], Albert CORTES[2], Francesc FERNÁNDEZ-AVILÉS[2], María SUÁREZ-LLEDÓ[2], Juan CORREA[2], Valentín ORTIZ-MALDONADO[2], Genoveva CUESTA[3], Nuria MARTINEZ-CIBRIAN[2], Jordi ESTEVE[2], María Ángeles MARCOS[3], Josep MENSA[1], Alex SORIANO[1], and Carolina GARCIA-VIDAL[1*], on behalf of "COVID-19-researcher group"[#].

[1] Department of Infectious Diseases, Hospital Clinic of Barcelona-IDIBAPS, University of Barcelona, Barcelona, Spain.

[2] Department of Haematology, Hospital Clinic of Barcelona-IDIBAPS, University of Barcelona, Barcelona, Spain.

[3] Department of Microbiology, Hospital Clinic, University of Barcelona, Barcelona, Spain.

*Contributed equally to this manuscript.

[#] Study Group team members are listed in the Acknowledgments section.

Running title: Antivirals in COVID-19 hematologic patients.

Corresponding author: Dr. Carolina Garcia-Vidal. Department of Infectious Diseases, Hospital Clinic of Barcelona. C/ Villarroel 170, 08036 Barcelona, Spain. Tel: (+34) 93-227-5400. Email: carolgv75@hotmail.com; cgarciav@clinic.cat.

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SYNOPSIS

Objectives: We aimed to describe the clinical outcomes and duration of viral shedding in high-risk patients with hematologic malignancies hospitalized with COVID-19 during Omicron variant predominance who received early treatment with antivirals.

Methods: We conducted a prospective observational study on high-risk hematologic patients admitted in our hospital between December 2021 and March 2022. We performed detection techniques on viral sub-genomic mRNAs until negative results were obtained to document active, prolonged viral replication.

Results: This analysis included 60 consecutive adults with high-risk hematologic malignancies and COVID-19. All of these patients underwent early treatment with remdesivir. 32 (53%) patients received combined antiviral strategies, with sotrovimab or hyperimmune plasma being added to remdesivir. The median length of viral replication — as measured by rRT-PCR and/or subgenomic RNAs detection — was 20 (IQR 14-28) days. Prolonged viral replication (six weeks after diagnosis) was documented in six (10%) patients. Only two patients had prolonged infection for more than two months. Overall mortality was 5%, while COVID-19-related mortality was 0%.

Conclusions: Current outcomes of high-risk patients with hematologic malignancies hospitalized with COVID-19 during Omicron variant are good with the use of early antiviral strategies. Persistent viral shedding has been uncommon.

INTRODUCTION

As an infectious disease, coronavirus disease 2019 (COVID-19) has emerged as a leading cause of death in patients with hematologic malignancies. Reported mortality rates have reached between 28-50% in high-risk hematologic patients like those with either acute leukaemia or other lymphoproliferative diseases, including those receiving CAR T-cell therapy.[1] Moreover, severely immunosuppressed patients with hematologic malignancies face an increased likelihood of presenting persistent viral shedding. [2–4] Consequently, patients experience delays in therapies for their haematological malignancies and clinical outcomes worsen as a result of such postponement. In addition, persistent viral replication for weeks or even months represents a risk for the selection of variants with mutations that potentially can escape from host immunity including the vaccine induced antibodies as well as the specifically designed monoclonal antibodies against Spike protein. [5] Finally, persistent SARS-CoV-2 infections make it difficult to manage patients with hematologic malignancies—either hospitalized or on an outpatient basis—increasing the risk of nosocomial outbreaks in wards, external consultations or day hospital. For all of these reasons, early antiviral treatment in these patients even in combination is conceptually highly appealing; it could prevent complications and improve clinical outcomes.

Unfortunately, information from clinical trials on COVID-19 antiviral efficacy in patients diagnosed with hematologic malignancies is scarce. To date, no specific randomized studies have described persistence in detail. Moreover, the current real-life situation with vaccinated patients with Omicron infection who had early diagnosis and treatment has been poor described. Since December 2021, the protocol of our institution includes early treatment with antivirals for high-risk hematologic patients. We aimed in the present study to describe the current clinical outcomes and duration of viral shedding in a cohort of high-risk patients with

hematologic malignancies, mostly adequately vaccinated, during a period dominated by the Omicron variant who received early treatment with antivirals.

MATERIALS AND METHODS

Study population, setting and definitions

This prospective observational study included all consecutive adults with high-risk hematologic malignancies in Hospital Clinic (Barcelona, Spain) and a SARS-CoV-2 Omicron variant infection diagnosis between December 2021 and March 2022. Since December 2021, we treated all high-risk patients with hematologic malignancies and a SARS-CoV-2 infection who presented a cycle threshold (Ct) value of less than 28 in rRT-PCR at COVID-19 diagnosis and/or duration of infection of less than ≤10 days from symptoms onset at admission. Antiviral treatment was remdesivir in all cases and we also administered hyperimmune plasma and/or sotrovimab when possible, that is, in accordance with Spanish law treatment regulation. Anti-inflammatory drugs (corticosteroids, baricitinib and tocilizumab), antibiotics, and/or anticoagulants were concomitantly administered when needed.

Hematologic malignancies were considered as high-risk when patients presented acute leukaemia, lymphoma in either treatment or remission with rituximab therapy, multiple myeloma, chronic lymphocytic leukaemia receiving biological therapies, and severe myelodysplastic syndrome in active treatment. Patients receiving CAR T-cell therapies or patients either within the first year following an allogenic hematopoietic stem cell transplantation or within the initial six months after an autologous stem cell transplant (ASCT) were also deemed as a high-risk group.

The outcomes of the study were mortality at the end of follow-up, and the need of intensive care unit admission, and the length of viral shedding.

The Institutional Ethics Committee of Hospital Clinic of Barcelona approved the study and due to the nature of the retrospective data review, waived the need for informed consent from individual patients (HCB/2020/0273).

Microbiological studies

We performed rRT-PCR testing on nasal and oropharyngeal swab specimens to confirm COVID-19 diagnoses for all subjects. All hematologic patients from the cohort underwent further testing until negativization to determine the duration of viral shedding. The Omicron variant was identified using a multiplex RT-PCR Allplex SARS-CoV-2 Variants I assay and II assay (Seegene Inc., Korea) and via the detection of SARS-CoV-2 HV69/70 deletion, N501Y, E484K, W152C, K417N, K417T and L452R mutations of the S gene. Patients with a prolonged positive rRT-PCR underwent further testing to identify viral sub-genomic RNA (sgRNA), as it is better correlated with active viral replication. [6]

Statistical analysis

Categorical variables were described using the absolute number and percentage, while continuous variables were presented using the median and interquartile range (IQR). Quantitative variables were compared with the Mann-Whitney U test. Statistical significance was defined as a p-value <0.05. Analyses were performed using Mac SPSS, version 28.0 (SPSS, Chicago, IL, USA).

RESULTS

A total of 60 high-risk patients with hematologic malignancies were diagnosed with a SARS-CoV-2 Omicron variant infection during the study period. Table 1 details the main patient characteristics. The median time from symptom onset to COVID-19 diagnosis was 1 (IQR 0-3) day; from COVID-19 diagnosis to hospital admission, 1 (IQR 0-5) day; and from COVID-19 diagnosis to antiviral treatment, 2 (IQR 1-5) days. The most common hematologic

malignancies were lymphoma diseases in active chemotherapy treatment (24 patients; 40%); acute leukaemia ongoing intensive chemotherapy (10, 16.7 %), multiple myeloma in active treatment (9, 15 %) and chronic lymphocytic leukaemia (9, 15 %). Among patients diagnosed by multiple myeloma, 7 (87.5%) received treatment with daratumumab prior to COVID-19 episode, and 5 (71.4%) were vaccinated with three doses. Prior vaccination was documented in 57 patients (95%), of whom 31 (51.7%) received three vaccine doses. Conversely, SARS-CoV-2 serology at admission was positive only in 25 patients (41.7%). Of these, 12 (48 %) had received three vaccine doses.

Most admitted patients presented fever, cough, and pharyngitis; however, 13.3 % were asymptomatic. A total of 17 patients (28.3 %) had radiological findings suggestive of SARS-COV-2 pneumonia and 17 patients (28.3 %) required oxygen therapy at disease onset. The median rRT-PCR cycle threshold (Ct) at admission was 19 (17-22). Most patients (96.6%) had Ct values under 28. Laboratory values were available for all patients of the cohort. Inflammatory markers were altered in 20 patients (33.3 %), of these 13 (21.7%) had C-reactive protein (CRP) > 8 mg/dL; 6 patients (10 %) and 10 patients (16.7 %) had elevation of ferritin (> 1000 ng/mL) and LDH (> 320 U/L) attributable to SARS-CoV-2 infection, respectively. Positive respiratory cultures suggestive of bacterial co-infection (*Haemophilus influenzae, Pseudomonas aeruginosa, Streptococcus pneumoniae*) were documented in 3 (5 %) patients. No significative differences were observed on laboratory values at admission according to evidence of bacterial co-infection. 18 patients had an infection caused by SARS-CoV-2 Omicron BA.1.1 variant. No patient had SARS-CoV-2 Omicron BA.2 variant infection.

All 60 patients received remdesivir. Median (IQR) length from symptom onset to remdesivir use was 2 (1-6) days. Hyperimmune plasma was administered to 32 (53.3%) patients, of whom 17 (53.1 %) presented a negative serology at admission. Sotrovimab was administered to 13

(21.7%) patients, of whom 9 (69.2 %) presented a negative serology at admission; and 10 patients had also received hyperimmune plasma. Median length from COVID-19 diagnosis to hyperimmune plasma and sotrovimab treatment was 4 (2-6) and 8 (5-16) days, respectively. Median (IQR) length of viral shedding—as measured by PCR and/or subgenomic RNAs detection—was 20 (14-28) days. Figure 1 details the median length of viral shedding in several different group of patients. Of the 31 patients with a negative SARS-CoV-2 serology, median (IQR) length of viral shedding was 20 (15-26) days. Of the 25 patients with positive SARS-CoV-2 serology, median (IQR) length of viral replication was 18 (11-29) days. A total of 22 (36.7 %) patients had viral shedding 21 days after diagnosis; 15 (25%) had viral shedding 28 days after diagnosis; and 6 (10%) had viral shedding 42 days after diagnosis. Three of these patients had recently received CAR T-cell therapy, while the other three had multiple myeloma. Table 2 details the characteristic of those patients with prolonged viral replication that lasted more than 42 days (six weeks) after diagnosis.

Median (IQR) length of viral shedding after treatment administration in patients who received remdesivir monotherapy was 16 (10-24) days; for those who received remdesivir and plasma, median (IQR) length was 17 (9-24) days (p = 0.7). Median (IQR) length of viral shedding in patients who received sotrovimab was 10 (5-21) days (p = 0.4).

A total of four (6.7%) patients required ICU admission, mainly due to respiratory failure and the need for high-flow oxygen. One patient needed mechanical ventilation. Within the first 60 days of SARS-CoV-2 infection, 3 (5%) patients died. One patient with myelofibrosis treated with ruxolitinib died on day 27 after COVID-19 diagnosis due to unrelated intravascular disseminated coagulation. The second patient (in palliative care) had Hodgkin lymphoma and end-stage renal cell carcinoma and died 35 days after COVID-19 infection. Cause of death was multiple organ failure due to septic shock triggered by *Escherichia coli* infection. Finally, the

last patient had Hodgkin lymphoma and end-stage chronic kidney disease and died four days after COVID-19 infection due to acute pulmonary oedema. All three patients were still positive for SARS-CoV-2 PCR at the time of death.

DISCUSSION

We reported extremely good outcomes in a cohort of high-risk patients with hematologic malignancies and COVID-19 Omicron variant infection who received both diagnosis and antiviral treatment early. Although most patients had been vaccinated, only half had a positive serology at infection onset. Some of these patients received combined antiviral strategies.

Several trials have demonstrated that early treatment with antiviral drugs or monoclonal antibodies can decrease progression of COVID-19 to severe disease and may also reduce SARS-CoV-2 viral load. [7–9] However, most trials included only a few high-risk patients with hematologic malignancies and were conducted before Omicron variants were in circulation—even before the Delta variant. Furthermore, most of the study subjects were from a non-vaccinated population.

In previous studies, our group described the importance of treating patients in a personalized manner depending on the phenotypic patterns of the diseases to diminish mortality: viral, inflammatory, thrombotic or co-infection. [10–12] Here, we report that all high-risk patients with hematologic malignancies had a viral phenotype with high viral loads; however, few presented an inflammatory or thrombotic pattern. For this reason, antiviral strategies are extremely important, and concomitant treatments with dexamethasone or other immunosuppressive therapy should be reserved for patients with a higher requirement for such approaches.

A high mortality ranging between 31-39% has been described in recent studies including an impressive number of patients with a variety of hematologic malignancies. [13,14] Marchesi *et al*.[15] reported a mortality rate of 46.4% in a recent published cohort of 388 patients with acute leukaemia and COVID-19. This mortality rate increased to 68% in patients diagnosed with acute leukaemia and COVID-19 simultaneously. Several series have documented mortality rates close to 30% in patients with chronic lymphocytic leukaemia and COVID-19. [16–18] A cohort of patients with COVID-19 receiving CAR T-cell therapy documented a mortality rate of 50%.[19] A very recent cohort of hematologic patients with Sars-Cov-2 Omicron infection, who have been prior vaccinated in 83% of cases, reported an overall mortality among hospitalized patients of 16.5% (51/309). [20] These results—far removed from the mortality figures described in the non-immunosuppressed population—demonstrate that high-risk patients with hematologic disorders require a personalized and perhaps more aggressive therapeutic strategy than the general population. In our series, mortality was 5%. COVID-19-related mortality was not observed, supporting the idea that early intensive antiviral strategies in this population are important. We also documented that this aggressive antiviral treatment significantly decreased persistent viral infection in our high-risk patients. This is of the upmost importance, as clinicians will need to be able to follow patients' chemotherapy treatments quickly; optimize routine visits; reduce the risk of outbreaks among immunocompromised patients in healthcare-related environments and perhaps—above all—avoid viral mutations. With our strategy, only six (10%) patients had viral persistence of SARS-CoV-2 six weeks after diagnosis, and only two (3%) tested positive more than two months after diagnosis. All of these patients had severe immunosuppression that affected different targets, especially B lymphocytes, CD20 and CD19.

The new oral antivirals against SARS-CoV-2—nirmaltrelvir-ritonavir and molnupiravir—may be an opportunity to facilitate early treatment of high-risk patients with hematologic malignancies. Targeted studies are required to both demonstrate prognosis following the use of these drugs in this population and decide if monotherapy or combined antiviral strategies is needed.

Our study has some limitations that should be noted. It is a unicentric study. It includes a full cohort of patients who were prospectively followed-up and in whom antiviral treatment differed due to varying attending physicians' decisions and treatment availability per regulatory Spanish law. However, we would highlight that all patients were monitored by the same infectious disease team, who shared the idea of early treatment and close follow-up using sgRNA as a surrogate marker of viral viability until negativization.

As a summary, early and aggressive antiviral treatment for SARS-CoV-2 in high-risk patients with hematologic malignancies and COVID-19 is associated with excellent outcomes and short viral shedding duration.

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307 *Table 1. Main epidemiological and clinical characteristics of admitted patients with hematologic malignancies and SARS-*
308 *CoV-2 infection.*
309

	N = 60
Patient characteristics	
Age, in years - Median (IQR)	61 (50-73)
Age > 65 years N (%)	26 (43.3)
Sex male, N (%)	34 (56.7)
Baseline hematologic malignancy N (%)	
Lymphoma*	24 (40)
Acute leukaemia	10 (16.7)
Multiple myeloma	9 (15)
Chronic lymphocytic leukaemia	9 (15)
Myelodysplastic syndrome	4 (6.7)
Others†	4 (6.7)
Last/ongoing treatment before COVID-19 N (%)	
Prior hematopoietic stem-cell transplantation	19 (31.7)
Allogenic hematopoietic stem-cell transplantation	16 (26.7)
Autologous hematopoietic stem-cell transplantation	3 (5)
Prior CAR T-cell therapy	8 (13.3)
Prior corticosteroid use (3 months)	20 (33.3)
Prior chemotherapy (3 months)	40 (66.7)
Prior rituximab use (12 months)	16 (26.7)
Other Comorbidities N (%)	
Arterial hypertension	23 (38.3)
Chronic heart disease	13 (21.7)
Chronic lung disease	9 (15)
Diabetes mellitus	8 (13.3)
Chronic renal failure	7 (11.7)
Chronic liver disease	2 (3.3)
Solid neoplasm	2 (3.3)
Symptoms of SarsCov2 N (%)	
Cough	34 (56.7)
Fever	29 (48.3)
Pharyngitis	29 (48.3)
Rhinorrhoea	13 (21.7)
Dyspnoea	12 (20)
Asymptomatic disease	8 (13.3)
Other clinical features N (%)	
Prior COVID-19 vaccination	57 (95)
Minimum of 3 doses of COVID-19 vaccination	31 (51.7)
Negative SARS-CoV-2 serology at admission	31 (51.7)
Current neutropenia (< 500/mm^3)	7 (11.7)
Long-term lymphopenia (> 1 month; < 900 lymphocytes/mm^3)	23 (38.3)

Vital signs at admission; Median (IQR)	
Temperature - (ºC)	36.2 (35.9-36.7)
Respiratory rate - (rpm)	18 (16-20)
Oxygen saturation – (%)	97 (95-98)
Laboratory values at admission; Median (IQR)	
Creatinine (mg/dL)	0.9 (0.7-1.1)
Ferritin (ng/mL)	517 (177 - 1216)
C-reactive protein (mg/dL)	3.5 (0.5-6.5)
Procalcitonin (ng/mL)	0.12 (0.08-0.20)
D-dimer (ng/mL)	450 (260-1180)
LDH (U/L)	241 (191-340)
Lymphocyte count (cells/mm^3)	650 (400-1100)
Viral cycle threshold of first rRT-PCR; *Median (IQR)*	19 (17-22)
rRT-PCR Ct range; N (%)	
- **Ct < 20**	41 (68.3)
- **Ct 21 – 28**	17 (28.3)
- **Ct > 28**	2 (3.3)
Treatment; N (%)	
Oxygen	17 (28.3)
High-flow nasal cannula	4 (6.7)
Remdesivir	60 (100)
Glucocorticoids	20 (33.3)
Baricitinib	4 (6.7)
Tocilizumab	14 (23.3)
Sotrovimab	13 (21.7)
Plasma	32 (53.3)
Antibiotics	41 (68)
Duration of Remdesivir treatment (days); Median (IQR)	9 (5-10)
Length of SARS-CoV-2 viability (days); Median (IQR)	20 (14-28)
SARS-CoV-2 viability longer than 21 days since diagnosis; N (%)	22 (36.7)
SARS-CoV-2 viability longer than 28 days since diagnosis; N (%)	15 (25)
Length of hospital stay (days); Median (IQR)	9 (6-14)
Intensive care unit admission; N (%)	4 (6.7)
Death; N (%)	3 (5)

Ct, cycle threshold

* follicular lymphoma in 9 (15%) patients; diffuse large B-cell lymphoma in 7 (11.7%); mantle cell lymphoma in 4 (6.7%); Hodgkin lymphoma in 2 (3.3%); hepatosplenic lymphoma in 1 (1.7%); high-grade lymphoma in 1 (1.7%).

† bone marrow failure (2 patients); myelofibrosis (1 patient); common variable immunodeficiency (1 patient)

Table 2. Main characteristics of patients with hematologic malignancies and prolonged viral shedding of more than six weeks.

Case	Sex, age (years)	Baseline disease and important risk factors	COVID-19 treatment	Days from first to last positive rRT-PCR	Clinical manifestation of prolonged infection	SARS-CoV-2 Serology	Outcomes
1	Male 73	Diffuse large B-cell lymphoma Prior CAR T-cell therapy Prior Rituximab	Remdesivir Corticoids - 3 doses of SARS-CoV-2 vaccine	104	none	Positive	Organizing pneumonia and recovery
2	Male 68	Acute leukaemia Prior CAR T-cell therapy Long-term lymphopenia	Remdesivir Convalescent plasma - 2 doses of SARS-CoV-2 vaccine	68	none	Positive	Recovery
3	Male 58	Multiple myeloma treated by Daratumumab.	Remdesivir Convalescent plasma Tocilizumab Oxygen - 3 doses of SARS-CoV-2 vaccine	46	fever, cough, rhinorrhoea, pharyngitis	Positive	Recovery
4	Male 47	Mantle cell lymphoma Prior CAR T-cell therapy	Remdesivir Tocilizumab Corticoids - 2 doses of SARS-CoV-2 vaccine	56	fever, cough, pharyngitis	Negative	Organizing pneumonia and recovery
5	Female 72	Multiple myeloma treated by Daratumumab	Remdesivir Convalescent plasma Sotrovimab Tocilizumab Corticoids Oxygen - 3 doses of SARS-CoV-2 vaccine	59	fever, dyspnoea, rhinorrhoea, pharyngitis	Negative	Organizing pneumonia and recovery
6	Female 73	Multiple myeloma treated by Daratumumab Prior corticosteroid use Long-term lymphopenia	Remdesivir Convalescent plasma Sotrovimab - 2 doses of SARS-CoV-2 vaccine	56	cough	Negative	Recovery

Figure 1. Length of viral replication in different study groups