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LETTER TO THE EDITOR

A cohort study of COVID-19 infection in pediatric oncology patients plus the utility and safety of remdesivir treatment

Rina Yue Ling Ong[a], Valerie Xue Fen Seah[a], Chia Yin Chong[b,c,d,e], Koh Cheng Thoon[b,c,d,e], Natalie Woon Hui Tan[b,c,d,e], Jiahui Li[b,c,d,e], Karen Donceras Nadua[b,c,d,e], Shui Yen Soh[c,d,e,f], Michaela Su-Fern Seng[c,d,e,f], Thi Ngoc Anh Pham[g], Chee Fu Yung[b,d,e*] and Kai-Qian Kam[b,c,d,e*]

[a]Department of Pharmacy, KK Women's and Children's Hospital, Singapore, Singapore; [b]Infectious Disease Service, Department of Pediatrics, KK Women's and Children's Hospital, Singapore, Singapore; [c]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; [d]Duke-National University of Singapore Medical School, Singapore, Singapore; [e]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore; [f]Haematology/Oncology Service, Department of Pediatrics, KK Women's and Children's Hospital, Singapore, Singapore; [g]Nursing Clinical Services, Division of Nursing, KK Women's and Children's Hospital, Singapore, Singapore

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Introduction

The World Health Organization (WHO) first declared the severe acute respiratory syndrome coronavirus-2 (SAR-CoV-2) a pandemic on 11 March 2020 [1]. Although children with COVID-19 infection generally present with mild form of the disease [2], oncology patients are considered at increased risk of hospitalization and death from COVID-19 [3,4]. They are also known to have prolonged shedding of SARS-CoV-2, which may have clinical and public health implications [5].

The PINETREE trial demonstrated that a short three-day course of remdesivir in high-risk adults with mild COVID-19 infection resulted in a lower risk of hospitalization or death [6]. However, use in high-risk pediatric patients with mild infection has not been definitively established. The aim of this study was to describe the clinical manifestation of COVID-19 infection in pediatric oncology patients and to evaluate the real-world utility and safety of remdesivir for the treatment of COVID-19 infection in this cohort.

Methods

Study Population

This retrospective cohort study was conducted in KK Women's and Children's Hospital in Singapore. We included all pediatric oncology patients $\leq$18 years of age, who were admitted from 1 November 2021 (first pediatric oncology COVID-19 case) to 31 March 2022. Patients who were fully vaccinated with COVID-19 vaccines at the point of SARS-CoV2-2 diagnosis were excluded. All cases were confirmed *via* SARS-CoV-2 real-time reverse transcriptase-polymerase chain reaction (PCR) and were undergoing immunosuppressive treatment. Disease severity was classified according to the National Institute of Health (NIH) COVID-19 guidelines [7].

Data Collection

Patient-specific data were obtained from the electronic hospital records. Degree of immunosuppression was adapted from Madhusoodhan et al. [8] The primary outcome studied was the time to viral clearance, defined as the time interval between the 1st positive PCR and the 1st of two consecutive negative PCRs. Other outcomes studied included time to PCR cycle threshold (Ct) $\geq$25 (defined as the time interval between the 1st positive PCR and the 1st PCR with Ct $\geq$25), days to defervescence (defined as attainment and sustenance of body temperature of $<$38 °C), progression to severe COVID-19 infection (based on the NIH severity criteria7], length of stay, and 30-day mortality. A surrogate marker of viral load with SARS-CoV-2 PCR is the Ct value, and a cutoff Ct value of $\geq$25 was selected as the standardized criteria for de-isolation of patients in our institution, given that infectivity is reduced when Ct values are $\geq$25 [9]. The study was approved by the Singhealth Centralized Institutional Review Board (CIRB 2020/2094). Written informed consent was waived in light of public health pandemic research.

Remdesivir treatment

Decision to initiate treatment with remdesivir was based on individual case's clinical condition. Remdesivir was initiated at a loading dose of 5 mg/kg/dose (maximum dose of 200 mg) on day one, and 2.5 mg/kg/dose Q24H (maximum dose of 100 mg) on days two and three, together with daily

CONTACT Rina Yue Ling Ong rina.ong.yl@kkh.com.sg Department of Pharmacy, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore; Chee Fu Yung yung.chee.fu@singhealth.com.sg Department of Paediatrics, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore
*These authors are contributed equally to the work.

monitoring of hepatic transaminases, baseline electrocardiogram, and continuous cardiac monitoring.

Statistical and data analysis

Independent t-test was used for comparison involving continuous variables. A p-value of $p < 0.05$ was considered statistically significant. SPSS statistical software (version 28.0, IBM, Illinois, USA) was used for data analyses. Cumulative frequency curves of the time to viral clearance and time to PCR Ct $\geq$25 were plotted.

Results

Clinical presentation

A total of 18 pediatric oncology patients were identified (Table 1). The distribution of immunosuppressive potential of the cohort was: Severe ($n = 4$, 22.2%), Moderate ($n = 9$, 50.0%) and Low ($n = 5$, 27.8%). The background diagnoses included lymphoma, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), neuroblastoma, post-haematopoietic stem cell transplant recipients, juvenile myelomonocytic leukemia, optic glioma, atypical teratoid/rhabdoid tumor (ATRT) and pilomyxoid astrocytoma. All patients had mild COVID-19 infection, based on the NIH disease severity classification [7]. The median PCR Ct value was 18.44 (IQR: 16.40 – 22.28) at time of diagnosis. Median time to viral clearance of the cohort was 31 days (IQR: 27 – 57) and time to PCR Ct value $\geq$25 was 7.0 days (IQR: 5.5 – 9.0).

Utility and safety of remdesivir

Remdesivir was initiated in four patients (lymphoma, AML and ALL) at a median of 3.5 days (IQR: 2.75 – 4) from symptom onset. The documented clinical indications for remdesivir initiation included: recent receipt of chemotherapy; to prevent delay of planned 2nd cycle high-dose chemotherapy with autologous stem cell rescue; persistent symptoms and repeat SARS-COV-2 PCR Ct <25. Baseline immunosuppressive potential was similar in the treated and non-treated groups ($p = 0.778$). There were no statistically significant differences in baseline laboratory parameters although ANC was lower in the remdesivir group (0.55×10^9 cells/L vs 0.76×10^9 cells/L, $p = 0.055$) (Table 1).

Figure 1 shows the cumulative frequency curves of the time to viral clearance, illustrating the proportion of patients with a negative SARS-CoV-2 PCR plotted against time. In terms of the point estimates of the median time to viral clearance, the median time was numerically longer in the remdesivir group but this was not statistically significant (45 days, vs 28 days, $p = 0.136$) with overlapping IQR.

Secondary outcomes such as time to PCR Ct $\geq$25 (7.5 days vs 6 days, $p = 0.694$), and days to defervescence (3.5 days vs 2 days, $p = 0.597$) were also similar between both groups. Length of stay was longer in the remdesivir group, but this difference was not statistically significant (7 days, vs 4.5 days, $p = 0.306$). This was due to one patient in the remdesivir group having inpatient chemotherapy after recovering from COVID-19. There were no reported remdesivir-related adverse events.

Table 1. Demographics, clinical presentation, and clinical outcomes.

	ALL (N = 18)		No Remdesivir (N = 14)		Received Remdesivir (N = 4)		p Value
DEMOGRAPHICS							
Male	13	(72.2%)	9	(64.3%)	4	(100.0%)	0.019
Age* (years)	6.50	(4.64, 9.83)	6.50	(4.83, 8.98)	6.54	(2.76, 10.25)	0.692
Weight* (kg),	19.45	(16.1, 30.00)	19.45	(16.65, 25.03)	31.0	(11.8, 50.75)	0.717
Body Mass Index, BMI (kg/ m^2)	16.3	(15.1, 19.6)	16.3	(15.1, 17.2)	18	(15, 20.93)	0.794
BMI-For-Age Percentiles (%)	65	(20, 77)	65	(23, 75)	54.5	(15.75, 90.75)	0.996
Immunosuppressive potential[a]							0.778
Severe	4	(22.2%)	3	(21.4%)	1	(25.0%)	
Moderate	9	(50.0%)	7	(50.0%)	2	(50.0%)	
Low	5	(27.8%)	4	(28.6%)	1	(25.0%)	
Days from last chemotherapy to date of COVID-19 diagnosis*	32	(12.5, 116.25)	27	(9.75, 116.25)	42.5	(28.75, 105)	0.810
CLINICAL PRESENTATION							
Respiratory symptoms prior to admission (days)*	1	(1, 3)	1.5	(1, 2.75)	1	(1, 1.25)	0.139
Fever prior to admission (days)*	1	(1, 1)	1	(0, 1)	1	(1, 1)	0.185
LABORATORY PARAMETERS							
SARS-COV-2 Cycle threshold (CT)*, lowest	18.44	(16.40, 22.28)	18.3	(16.4, 22.03)	20.3	(17.59, 22.03)	0.648
C-reactive protein (mg/L)*, highest	5.50	(3.45, 15.65)	5.5	(3.45, 12.30)	9.4	(5.65, 16.55)	0.474
Lactate dehydrogenase (U/L)*, highest	232.50	(220.25, 247.75)	231	(228, 234)	250	(218, 287.5)	0.583
Ferritin (ug/L)*, highest	912.6	(679.8, 1369.8)	1016	(826.15 1808.7)	1149	(648.5, 9493.7)	0.423
D-dimer (mg/L FEU)*, highest	0.83	(0.61, 1.14)	0.56	(0.41, 0.77)	1.11	(0.89, 5.71)	0.361
Absolute neutrophil count (ANC) ($x10^9$ cells/L)*[d], lowest	0.74	(0.61, 1.59)	0.76	(0.67, 2.31)	0.55	(0.475, 0.79)	0.055
Absolute lymphocyte count ($x10^9$ cells/L)*, lowest	0.78	(0.54, 1.38)	0.96	(0.57, 1.55)	0.66	(0.465, 0.93)	0.193
CLINICAL OUTCOMES							
Progression to severe COVID-19 infection	0	(0.0%)	0	(0.0%)	0	(0.0%)	NA
Time to viral clearance (days)*	31	(27, 57)	28	(27, 36)	45	(30.25, 59.5)	0.136
Time to SARS-CoV2-PCR CT $\geq$25 (days)*	7	(5.5, 9)	6	(5.5, 9.5)	7.5	(4.75, 8.75)	0.662
Days to defervescence*	2.5	(1.75, 4.25)	2	(1.75, 4.25)	3.5	(1.5, 5.5)	0.597
Length of stay (days),*	6	(3, 8.5)	4.5	(3, 8.25)	7	(6.25, 24.25)	0.306
30-day mortality	0	(0.0%)	0	(0.0%)	0	(0.0)	NA

All data *n* (%), *(median (lower quartile, upper quartile).

[a]**Immunosuppressive potential: Grading based on degree of immunosuppression for most recent course of chemotherapy as detailed in the Methods section.**

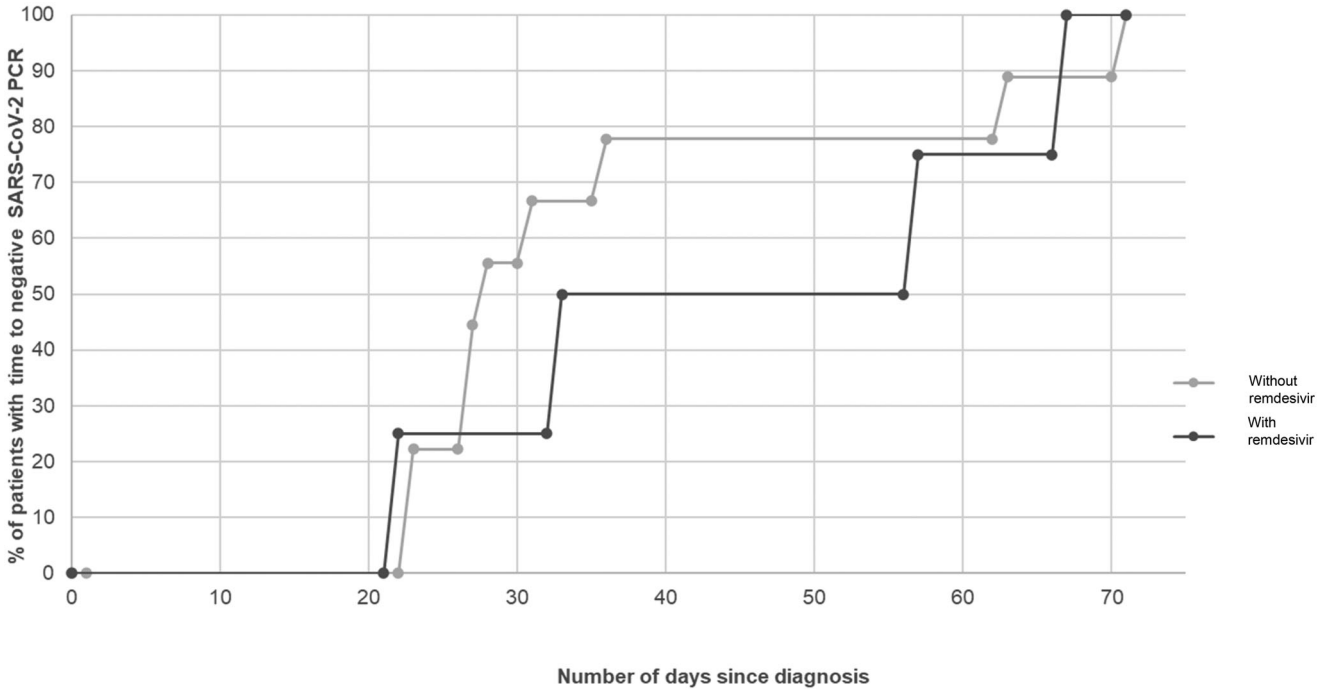

Figure 1. Cumulative percentage frequency curve of time to negative SARS-CoV-2 PCR (in days).

Discussion

Our cohort of pediatric oncology COVID-19 cases had mild disease at diagnosis and none progressed to severe disease or COVID-19 attributable deaths. We did not detect any clear benefit in terms of time to viral clearance or PCR Ct $\geq$25 between the treated versus non-treated groups, but our study findings are limited by its small sample size. Remdesivir was well tolerated in four of our pediatric oncology patients with no safety concerns detected.

Data on COVID-19 infection in pediatric oncology patients is currently limited to multi-national case series conducted in various waves of the pandemic [8,10–14]. Although severe cases have also been described in some immunocompromised children, the majority had mild infection [15–18]. In our study, all patients had a mild course of COVID-19 which could be attributed to most of our cases being diagnosed during the Omicron wave where the Omicron variant had been reported to cause less severe disease compared to earlier variants.

Thus far, there have only been four cohort studies of remdesivir use for the treatment of mild COVID-19 in adult immunocompromised patients [19–22]. At the time of writing, our study provides the only direct clinical experience on the use of remdesivir for the treatment of COVID-19 in pediatric oncology patients. No patients in either group reported viral clearance in the first 21 days of infection (Figure 1). Persistent viral shedding has been reported in both immunocompromised children and adults [23–25], as compared to a shorter duration of 16 to 17 days in healthy children [26–28]. This is in keeping with our current cohort with viral shedding of up to 71 days, with impaired B-cell and T-cell function being postulated to be the main reason for their inability to clear the virus [5,24,25].

The public health implications of variant evolution in these immunocompromised patients with prolonged viral shedding is a major cause for concern. Rapid viral evolution has also been described, with such patients having more transmissible or pathogenic SARS-CoV-2 escape variants over the entire course of their infection [29]. Unfortunately, the evidence for remdesivir in accelerating viral clearance remains inconclusive in our cohort. There is hence an urgent need for larger multi-institution studies in pediatric oncology children to evaluate the impact of other treatment modalities on the time to viral clearance.

Limited data suggested that remdesivir was generally well-tolerated [30–33], although severe adverse effects such as sinus bradycardia have been reported previously [34–36]. Our small study provided real-world data that remdesivir use was well-tolerated in immunosuppressed pediatric oncology patients. More safety data in such high risk cohorts are needed.

Our study has several limitations. It was a small retrospective, observational study and most patients were admitted during the Omicron wave of the pandemic. We could not adjust for baselines differences in disease status or immunosuppression due to the small sample size. However, the immunosuppressive potential distribution was similar between both groups. SARS-CoV-2 PCR testing was performed at the clinical discretion of the medical team, which may result in ascertainment bias. More testing in the non-treated group could potentially increase the likelihood of detection of clearance or SARS-CoV-2 PCR Ct $\geq$25. Time to viral clearance was assessed *via* SARS-CoV-2 PCR which

detects only viral RNA and may have poor correlation to viral infectivity [37].

Conclusion

In our observational cohort of immunocompromised pediatric oncology children with mild COVID-19 disease, we found the median time to viral clearance was 31 days which was much higher than observed in healthy children. Treatment with remdesivir in our cohort was safe but did not lead to early clearance of SARS-CoV-2 or shorter time to PCR Ct $\geq$25. There is an urgent need for larger clinical studies of SARS-CoV-2 infection and treatment efficacy in immunocompromised pediatric patients with mild COVID-19 infections, in view of the high risk of emergence of variants from the cohort.

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Ethical Approval

The study was approved by the Singhealth Centralized Institutional Review Board (CIRB 2020/2094). Written informed consent was waived in light of public health pandemic research, as the study involved was a non-interventional retrospective medical records review and the clinical management of patients was not affected. The research was conducted in compliance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice. Precaution was taken to protect the privacy of research subjects and the confidentiality of their personal information. Any articles or data including information which could potentially identify an individual are excluded from the publication of this manuscript.

Disclosure statement

The authors of this study declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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ORCID

Rina Yue Ling Ong http://orcid.org/0000-0003-1599-619X
Valerie Xue Fen Seah http://orcid.org/0000-0002-7775-6987
Chia Yin Chong http://orcid.org/0000-0003-3919-3324
Koh Cheng Thoon http://orcid.org/0000-0002-2844-010X
Natalie Woon Hui Tan http://orcid.org/0000-0002-7380-5008
Karen Donceras Nadua http://orcid.org/0000-0002-1313-7458
Shui Yen Soh http://orcid.org/0000-0002-4237-8904
Michaela Su-Fern Seng http://orcid.org/0000-0002-6245-2446
Chee Fu Yung http://orcid.org/0000-0001-9605-7690
Kai-Qian Kam http://orcid.org/0000-0002-2402-7262

Data Availability statement

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 restrictions (their containing information that could compromise the privacy of research participants).

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