



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

Note

Short-course remdesivir for healthcare-associated COVID-19: Case series from a non-acute care hospital

Yu Takahashi^a, Hideaki Wakita^a, Takuma Ishihara^b, Hideto Okazaki^c, Akihiro Ito^d, Mitsunaga Iwata^e, Shigeru Sonoda^h, Yohei Doi^{f,g,*}^a Department of Internal Medicine, Fujita Health University Nanakuri Memorial Hospital, Tsu, Mie, Japan^b Innovative and Clinical Research Promotion Center, Gifu University Hospital, Yanagido, Gifu, Japan^c Department of Liaison Rehabilitation Medicine, Fujita Health University School of Medicine, Tsu, Mie, Japan^d Department of Surgery and Palliative Medicine, Fujita Health University School of Medicine, Tsu, Mie, Japan^e Department of Emergency and General Internal Medicine, Fujita Health University School of Medicine, Toyoake, Aichi, Japan^f Departments of Microbiology and Infectious Diseases, Fujita Health University School of Medicine, Toyoake, Aichi, Japan^g Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA^h Department of Rehabilitation Medicine II, Fujita Health University School of Medicine, Tsu, Mie, Japan

ARTICLE INFO

Keywords:

Remdesivir
Drug therapy
COVID-19
R
ehabilitation
p
alliative care

ABSTRACT

Healthcare-associated COVID-19 among vulnerable patients leads to disproportionate morbidity and mortality. Early pharmacologic intervention may reduce negative sequelae and improve survival in such settings. This study aimed to describe outcome of patients with healthcare-associated COVID-19 who received early short-course remdesivir therapy. We reviewed the characteristics and outcome of hospitalized patients who developed COVID-19 during an outbreak that involved two wards at a non-acute care hospital in Japan and received short-course remdesivir. Forty-nine patients were diagnosed with COVID-19, 34 on a comprehensive inpatient rehabilitation ward and 15 on a combined palliative care and internal medicine ward. Forty-seven were symptomatic and 46 of them received remdesivir. The median age was 75, and the median Charlson comorbidity index was 6 among those who received it. Forty-one patients had received one or two doses of mRNA vaccines, while none had received a third dose. Most patients received 3 days of remdesivir. Of the patients followed up to 14 and 28 days from onset, 41/44 (95.3%) and 35/41 (85.4%) were alive, respectively. Six deaths occurred by 28 days in the palliative care/internal medicine ward and two of them were possibly related to COVID-19. Among those who survived, the performance status was unchanged between the time of onset and at 28 days.

COVID-19 causes disproportionately high mortality among the elderly with multiple comorbidities [1]. In an analysis of nationwide registry conducted early in the pandemic in Japan, in-hospital mortality of COVID-19 patients 65 years or older was 11.5% [2]. In particular, outbreaks in non-acute care healthcare settings constitute significant portions of COVID-19-related deaths, with an estimated case-fatality rate of approximately 16% among long-term care facility residents in both the United States and Japan [3]. In palliative care, a case-fatality rate exceeding 80% has been reported from the pre-vaccination period [4]. Among COVID-19 patients with high risk for severe disease and death, early pharmacologic intervention has been shown to significantly reduce these outcomes [5–9]. However, implementation of such strategy can be challenging due to limitations in available resources and

medications in non-acute care settings.

In February 2022, we experienced an outbreak of COVID-19 at a 218-bed non-acute care hospital in Japan, which consists of comprehensive inpatient rehabilitation wards and a combined palliative care and internal medicine ward with an average length of stay of 50 days. The affected patients were in one of the rehabilitation wards and the palliative care/internal medicine ward, and all were considered to be at high risk for severe disease and death. Short-course (3-day) remdesivir therapy had just been acknowledged in the national COVID-19 treatment guideline as a treatment option for patients with early-stage COVID-19 who are at high risk for severe disease or death (e.g. age 60 or greater) based on the PINETREE trial results at the time [5]. As all patients qualified as high risk, they were started on remdesivir as they

* Corresponding author. Departments of Microbiology and Infectious Diseases, Fujita Health University School of Medicine 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi, 470-1192, Japan.

E-mail address: yoheidoi@fujita-hu.ac.jp (Y. Doi).

<https://doi.org/10.1016/j.jiac.2022.08.025>

Received 30 June 2022; Received in revised form 15 August 2022; Accepted 26 August 2022

Available online 13 September 2022

1341-321X/© 2022 Japanese Society of Chemotherapy and The Japanese Association for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

became symptomatic and had a positive COVID-19 test. Here, we summarize the patient characteristics and their outcomes within the month following onset of COVID-19.

Patients admitted to the hospital and tested positive for COVID-19 in February 2022, either by PCR or rapid antigen, were included. The patients' demographics, Charlson comorbidity index at onset, vaccination status, symptoms, duration of remdesivir therapy, survival at 14 and 28 days from onset were extracted from the electronic medical records. Eastern Cooperative Oncology Group (ECOG) performance status was also recorded at onset, 14 days from onset, and 28 days from onset [10]. Descriptive statistics were performed using median and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. For estimating 14- and 28-day survival rates, the Kaplan-Meier method was used. Survival rates by age and malignancy were expressed using Kaplan-Meier curves. All statistical analyses were performed with the use of R 4.1.1 (The R Project for Statistical Computing).

A total of 49 patients had a positive COVID-19 test during this period. In the outbreak described here which occurred in a non-urban area at the height of the Omicron surge, no additional acute care capacity was available in the vicinity after the first two patients were transferred, which necessitated management of the additional patients on site. At the time, the Japanese government had just included short-course remdesivir as a treatment option in its COVID-19 management guideline. Since remdesivir was the only COVID-19 agent that was readily available without restrictions, patients were treated with this agent as soon as they developed symptoms consistent with COVID-19 and the diagnosis was confirmed by a positive test. Thirty-four of them were on the rehabilitation ward, and 15 of them were on the palliative care/internal medicine ward. Three of them did not receive remdesivir and were excluded from the analysis. The reasons for not receiving remdesivir were immediate transfer to an acute care hospital (2 patients) and impaired renal function (1 patient). The remaining 46 patients who received at least one dose of remdesivir constituted the cohort for this study. The demographics and remdesivir therapy administered are described in Table 1. The median age was 75, and 41 had received at least one dose of mRNA vaccine. While the timing of vaccination was unknown, most of them likely received the doses more than six months earlier, since the age group (60 years old and greater) was largely vaccinated by the end of July 2022 in Japan. However, none had received the third dose. The median Charlson comorbidity index was 6, which corresponds to an

estimated background 10-year survival of 2%. Documented COVID-19-related symptoms included fever (39 patients), sore throat (17 patients), cough (17 patients), headache (5 patients) and fatigue (2 patients). Based on the COVID-19 severity classification system adopted in Japan, 34 patients had mild disease (i.e. not requiring supplemental oxygen), 12 patients had moderate disease (i.e. requiring supplemental oxygen), and none had severe disease (i.e. requiring mechanical ventilation). Only one patient was asymptomatic. In all except one patient, remdesivir was started within 2 days from the symptom onset (positive test in the case of the one asymptomatic patient) and administered for a median of 3 days.

The median time from onset to resolution of symptoms was 4 days (IQR, 2–7). Two patients were discharged prior to 14 days, and an additional 3 patients were discharged prior to 28 days. Of the patients followed up to 14 and 28 days from onset, 41/44 (95.3%) and 35/41 (85.4%) were alive, respectively. All 6 deaths occurred among patients on the palliative care/internal medicine ward who had advanced malignancy (lung cancer [2], pancreatic cancer [2], colon cancer [1], renal cancer [1]). Additionally, two and one patients had history of diabetes and stroke, respectively. They all developed moderate disease, with SpO₂ at room air ranging between 86 and 94%. Two of these deaths were possibly related to COVID-19, where one patient had cardiac arrest of undetermined cause and the other patient expired from respiratory failure. The remaining 4 deaths were deemed to have been due to underlying illnesses and unrelated to COVID-19. Specifically, all patients who died were both age 70 or greater and had malignancy (Fig. 1). While information is limited in the literature, COVID-19 in inpatient palliative care settings has been associated with extremely high mortality [4,11]. In contrast, all patients on the rehabilitation ward were alive at 28 days.

Even when these vulnerable patients survive COVID-19, cognitive and functional decline is commonly observed. In this cohort, the median performance status score was 3 at onset, 14 days and 28 days (Table 2). Most patients maintained the same performance score over the course of 28 days, and none of the surviving patients had a decline in the performance status score of greater than one. This suggests that the negative impact on the functional levels of those who survived the infection was minimal.

In terms of safety, short-course remdesivir was generally well tolerated. Three patients developed transient liver function test abnormalities, one patient developed transient renal function abnormality, and one patient had itching at the infusion site.

Institutional outbreaks in non-acute care settings have accounted for a significant portion of morbidity and mortality over the course of the COVID-19 pandemic thus far, including in Japan [3]. Vaccination has dramatically reduced the risk of severe disease and deaths across age groups, but waning protection over time has been recognized as a major concern especially among the elderly [12], and the advent of the Omicron variant has further compromised the efficacy conferred by two doses of vaccines [13]. In this context, uncertainties remain over the risk of severe disease and death for vulnerable patients hospitalized in non-acute care settings. We acknowledge that a major limitation of our study is the lack of untreated patients as this was not a controlled clinical study, and we were not able to find such data in the literature, either. Though not directly comparable, a study from the U.K. in the Omicron period reported a 28-day mortality rate of 5.48% among long-term care facility residents with COVID-19, the majority of whom were either previously infected or received a booster vaccination, down from 10.75% in the pre-Omicron era [14].

During surges of infection, transferring patients from non-acute care settings to acute care hospitals can be challenging when the latter are also overwhelmed with excessive demand. The approach described here, where high-risk COVID-19 patients are identified and treated expeditiously, may represent the most effective and realistic COVID-19 care in non-acute care settings during such periods especially among those who have not received a booster vaccination. While remdesivir is available

Table 1
Patient demographics and remdesivir therapy.

Variable	n = 46 ^a
Ward	
Palliative care/internal medicine	14 (30.4%)
Rehabilitation	32 (69.6%)
Age	75 (70, 80)
Sex	
Female	19 (41.3%)
Male	27 (58.7%)
Vaccination	
One dose	1 (2.2%)
Two doses	40 (87.0%)
None	5 (10.9%)
Charlson comorbidity index	6.0 (5.0, 7.0)
Performance status at onset	
1	3 (6.5%)
2	15 (32.6%)
3	21 (45.7%)
4	7 (15.2%)
Days of remdesivir therapy	3.0 (3.0, 3.8)
Days from onset to first dose of remdesivir	
0	27 (58.7%)
1	18 (39.1%)
2	1 (2.2%)

^a n (%); Median (IQR).

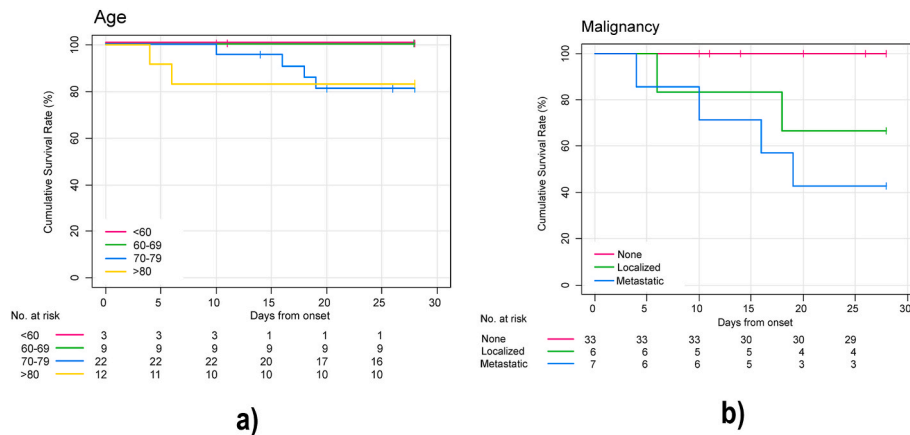


Fig. 1. 28-day survival curves of patients who were treated with remdesivir, stratified by age group (a) and presence of malignancy (b).

Table 2

Performance status scores at onset, 14 days and 28 days.

Score	Onset (n = 46)	14 days (n = 41)	28 days (n = 35)
1	3 (6.5%)	3 (7.3%)	2 (5.7%)
2	15 (32.6%)	11 (26.8%)	14 (40.0%)
3	21 (45.7%)	20 (48.8%)	16 (45.7%)
4	7 (15.2%)	7 (17.1%)	3 (8.6%)

only as an intravenous infusion, future advent of safe and potent oral antiviral agents may make this approach more generalizable.

Funding

Statistical analysis was supported in part by a grant from the Japan Agency for Medical Research and Development (AMED) under Grant Number 20fk0108150s0001.

Ethical approval

This study was approved by the Institutional Review Board of Fujita Health University, which provides ethics oversight for this hospital.

Author contributions

Y. Takahashi: Data curation, Writing – review & editing. H. Wakita: Writing – review & editing. T. Ishihara: Data analysis, Visualization. H. Okazaki: Writing – review & editing. A. Ito: Writing – review & editing. M. Iwata: Conceptualization, Writing – review & editing. S. Sonoda: Writing – review & editing. Y. Doi: Conceptualization, Data curation, Writing – review & editing.

Declaration of competing interest

Y.D. has served on an advisory board of, and received a speaking fee from, Gilead Sciences, the manufacturer of remdesivir. The other

authors declare that they have no conflicts of interests.

Acknowledgment

We thank Terumi Kinoshita for her support of infection control activities during the outbreak period.

References

- [1] Prendki V, Tiseo G, Falcone M, ESGfit Elderly. Caring for older adults during the COVID-19 pandemic. *Clin Microbiol Infect* 2022;28(6):785–91.
- [2] Asai Y, Nomoto H, Hayakawa K, et al. Comorbidities as risk factors for severe disease in hospitalized elderly COVID-19 patients by different age-groups in Japan. *Gerontology* 2022;1–11.
- [3] Abe K, Kawachi I. Deaths in nursing homes during the COVID-19 pandemic - lessons from Japan. *Healthc Pap* 2021;20(1):78–81.
- [4] de Oliveira LC, Rosa K, Durante AL, et al. Palliative care and COVID-19 pandemic: retrospective study of factors associated with infection and death at an oncological palliative care reference center. *Am J Hosp Palliat Care* 2021;38(5):512–20.
- [5] Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe covid-19 in outpatients. *N Engl J Med* 2022;386(4):305–15.
- [6] Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody combination and outcomes in outpatients with covid-19. *N Engl J Med* 2021;385(23):e81.
- [7] Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med* 2021;385(21):1941–50.
- [8] Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with covid-19. *N Engl J Med* 2022;386(15):1397–408.
- [9] Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. *N Engl J Med* 2022;386(6):509–20.
- [10] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative Oncology group. *Am J Clin Oncol* 1982;5(6):649–55.
- [11] de Oliveira LC, da Costa Rosa KS, Borsatto AZ, de Oliveira LAF, de Freitas R, Dos Santos Machado Sampaio SG. Prognostic factors in patients with advanced cancer and COVID-19: a cohort from the palliative care unit of the Brazilian national cancer institute. *Support Care Cancer* 2021;29(10):6005–12.
- [12] Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity after the BNT162b2 vaccine in Israel. *N Engl J Med* 2021;385(24):e85.
- [13] Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med* 2022;386(16):1532–46.
- [14] Krutikov M, Stirrup O, Nacer-Laidi H, et al. Outcomes of SARS-CoV-2 omicron infection in residents of long-term care facilities in England (VIVALDI): a prospective, cohort study. *Lancet Healthy Longev* 2022;3(5):e347–55.