Original article

Early cidofovir administration might be associated with a lower probability of respiratory failure in treating human adenovirus pneumonia: a retrospective cohort study

J.-H. Ko [1], J.U. Lim [2], J.Y. Choi [3], H.S. Oh [4], H. Yoo [5], B.W. Jhun [5], K. Huh [1], K.R. Peck [1, *]

[1] Division of Infectious Diseases, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[2] Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[3] Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, St Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Republic of Korea
[4] Division of Infectious Diseases, Department of Internal Medicine, Armed Forces Capital Hospital, Seongnam, Republic of Korea
[5] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

ARTICLE INFO

ABSTRACT

Objective: To compare outcomes of early and delayed treatment with cidofovir for human adenovirus (HAdV) pneumonia.
Methods: A retrospective cohort study in Korean military hospitals was conducted between January 2012 and December 2018. Patients with potentially severe HAdV pneumonia with risk factors for respiratory failure were included and divided into early (within 7 days from symptom onset) and delayed (after 7 days from symptom onset) treatment groups. The primary outcome was respiratory failure development within 21 days after symptom onset.
Results: A total of 89 patients with potentially severe HAdV pneumonia were enrolled in the cohort; they included 62 early and 27 delayed treatment patients. All patients were males in their early 20s. Significantly fewer patients in the early treatment group progressed to respiratory failure (8/62, 12.9%), compared to the delayed group (18/27, 66.7%, p < 0.001). Early treatment was associated with a lower 21-day probability of respiratory failure by the Kaplan—Meier method (p < 0.001). On multivariate analysis, monocyte count, hypoxaemia, confusion, whole lung involvement, and early cidofovir treatment within 7 days from symptom onset were included, and monocyte count (HR 0.995, 95%CI 0.991—1.000, p 0.042), confusion (HR 4.964, 95%CI 1.189—20.721, p = 0.028), and early cidofovir treatment (HR 0.319, 95%CI 0.115—0.883, p = 0.028) were significantly associated with respiratory failure.
Conclusions: Early administration of cidofovir was associated with a lower hazard for respiratory failure development. It is suggested that cidofovir be administered within 7 days from symptom onset to prevent respiratory failure in patients with potentially severe HAdV pneumonia. **J.-H. Ko, Clin Microbiol Infect 2020;26:646.e9—646.e14**

Introduction

Respiratory illnesses caused by the human adenovirus (HAdV) generally occur in infants and children [1], but severe, potentially fatal pneumonia is also reported in the adult population [2]. HAdV pneumonia in adults has been most frequently reported in communal living populations, especially among military trainees [3—8]. HAdV type 55 (HAdV-55), an emerging recombinant strain

of types 11 and 14 [9], has spread rapidly throughout China since the first Chinese outbreak in 2006 [7—10]. HAdV-55 has also been noticed in the Korean military from 2012 and caused a large outbreak beginning in the winter of 2014 [6,11—13]. This non-vaccine-type HAdV outbreak is currently ongoing in the Korean military, with a high burden of morbidity and mortality [13]. In managing severe HAdV pneumonia patients in the Korean military, we tried cidofovir based on previous case reports and *in vitro* studies [14—16], and we experienced several successes with early administration of cidofovir [17]. Since then, we have routinely administered cidofovir for all patients with potentially severe HAdV pneumonia and risk factors for respiratory failure [18], but the administration interval from symptom onset varied between patients. To compare outcomes of early and delayed treatment, we conducted a retrospective cohort study in Korean military hospitals for a 7-year period.

Methods

Study design and patient selection

A retrospective cohort study was performed. We reviewed electronic medical records of cidofovir-treated HAdV pneumonia patients at 14 military hospitals between January 2012 and December 2018. Among the cidofovir-treated HAdV pneumonia patients, we included patients with potentially severe disease who had any of the following risk factors for respiratory failure at initial presentation [18]: (a) hypoxaemia (PaO_2 <60 mmHg or SpO_2 <90%), (b) monocytopenia (<150/μL), (c) multilobar involvement (three or more lobes on chest computed tomography (CT)), or (d) pleural effusion on chest CT. Included patients were divided into an early treatment group (within 7 days from symptom onset) and a late treatment group (after 7 days from symptom onset), based on the median value of the cohort. The primary outcome was the development of respiratory failure within 21 days after symptom onset. Secondary outcomes included duration of hospital stay, intensive care unit (ICU) care, duration of ICU care, continuous renal replacement therapy (CRRT) support, extracorporeal membrane oxygenation (ECMO) support, and death. Secondary outcomes were assessed during the hospital stay of patients. It was generally recommended to administer cidofovir at a dosage of 5 mg/kg weekly in combination with oral probenecid [17]. Since the second dose of cidofovir was selectively administered among patients who progressed to respiratory failure, we evaluated outcomes associated with the first dose. This study was approved by the Institutional Review Board of the Armed Forces Medical Command (AFMC-19-IRB-099) and informed consent was waived by the board.

Data collection and definitions

Collected data included demographics, presenting symptoms, initial laboratory findings, factors for pneumonia severity measures, initial radiological findings, data on cidofovir and antibiotic treatment, underlying comorbidity, and outcomes. Quantitative variables were used as continuous variables and/or converted into categorical variables using commonly used cut-off values (presented in the results). CURB-65 score was used for the calculation of pneumonia severity [19], and the modified Medical Research Council (mMRC) scale for rating dyspnoea [20]. Initial presentation was assessed on the day of the first hospital visit. All included patients first visited the hospital after pneumonia development and were admitted on the same day. HAdV infections were confirmed by multiplex respiratory virus polymerase chain reaction (PCR)

tests using patients' sputum samples, as previously described [13]. Pneumonia was defined as the presence of parenchymal infiltration on chest x-ray or CT with respiratory symptoms. All included patients underwent chest CT unless whole lung involvement was apparent on chest x-ray. Respiratory failure was defined when mechanical ventilation (MV) support was required with a PaO_2/FiO_2 ratio $\leq$200 mmHg measured after endotracheal intubation. Renal impairment occurring within 2 weeks of cidofovir treatment was assessed according to the RIFLE (risk, injury, failure, loss and end-stage) criteria [21].

Statistical analysis

To compare clinical factors, either the Student's *t*-test or the Mann—Whitney U test was used for continuous variables, and either the χ-square or Fisher's exact tests was used for categorical variables. The Kaplan—Meier method was used to calculate the 21-day probability of respiratory failure. The Cox proportional hazard model was used to evaluate potential risk factors for respiratory failure within 21 days. All factors clinically relevant to the outcome were evaluated by univariate analysis, and statistically significant factors were included in the multivariate analysis to adjust early administration of cidofovir within 7 days after symptom onset. If more than two factors that share parameters or are clinically correlated were statistically significant, only one factor with the strongest HR by univariate analysis was included in the multivariate analysis. A subgroup analysis was conducted among patients who received cidofovir before the development of respiratory failure. Patients who received cidofovir on the same day as or after respiratory failure development were excluded, and the primary outcome was evaluated with the same statistical methods. Missing data are presented in footnotes to the Tables. All p-values were two-tailed, and those <0.05 were considered statistically significant. IBM SPSS Statistics version 20.0 (IBM, Armonk, NY, USA) was used for all statistical analyses.
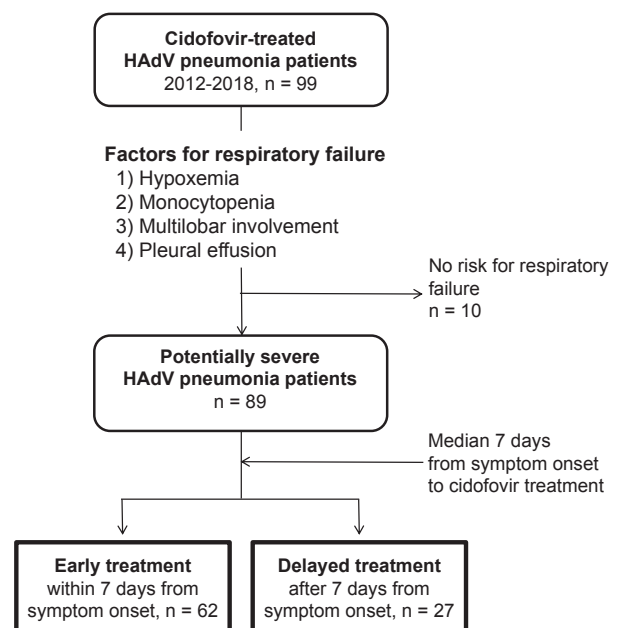
Fig. 1. Patient selection for the retrospective cohort. Patients who did not have any risk factors for respiratory failure were excluded. Patients were divided into early ($\leq$7 days from symptom onset) and delayed (>7 days from symptom onset) treatment groups, based on the median value of the cohort. HAdV, human adenovirus.

Results

Baseline characteristics and initial presentation

During the study period, a total of 89 patients were included in the cohort and were divided into early ($n = 62$) and delayed ($n = 27$) treatment groups (Fig. 1). Baseline characteristics and initial presentations of cidofovir-treated HAdV pneumonia patients are presented in Table 1. All patients were males in their early 20s. Presenting symptoms and laboratory findings did not differ between the two groups. Patients in the early treatment group visited the hospital earlier than those in the delayed group (mean 3.0 versus 5.4 days from symptom onset, p 0.001). Patients in the delayed treatment group had lower PaO_2/FiO_2 ratios and were more likely to have hypoxaemia compared to those in the early treatment group (both p < 0.001), while factors for CURB-65 did not differ. Among radiological findings, significantly more patients in the delayed treatment group presented with whole lung involvement (11/27, 40.7%) than those in the early treatment group (8/62, 12.9%, p 0.003). In addition to HAdV, other respiratory viruses were

co-detected in five patients in the early treatment group (5/62, 8.1%) and two patients in the delayed treatment group (2/27, 7.4%).

Treatment and outcomes

Factors associated with treatment and outcomes are presented in Table 2. All the included patients were followed for at least 21 days from symptom onset for outcome assessment (median 23 days). Compared to the early treatment group, significantly more patients in the delayed treatment group progressed to respiratory failure within 21 days after the onset of symptoms (8/62, 12.9% versus 18/27, 66.7%; p < 0.001). Among patients who progressed to respiratory failure, significantly more patients in the delayed treatment group exhibited late progression to respiratory failure after 7 days from symptom onset compared to those in the early treatment group (16/18, 88.9% versus 3/8, 37.5%; p 0.014). The duration of hospital stay and ICU care were significantly longer in the delayed treatment group than in the early treatment group (both p < 0.05). Significantly more patients in the delayed treatment group received ECMO support than in the early treatment

Table 1
Baseline characteristics and initial presentation of cidofovir-treated patients with human adenovirus (HAdV) pneumonia

Variables	Early treatment, within 7 days from symptom onset ($n = 62$)	Delayed treatment, after 7 days from symptom onset ($n = 27$)	*p* value
Demographics:			
Age, years	20.4 ± 1.4	20.4 ± 2.0	0.980
Male sex	62 (100)	27 (100)	NA
Presenting symptoms:			
Fever	62 (100)	27 (100)	NA
Cough	62 (100)	26 (96.3)	0.303
Sputum	59 (95.2)	25 (92.6)	0.637
Dyspnoea (MMRC > II)	28 (45.2)	13 (48.1)	0.795
Diarrhoea	21 (33.9)	7 (25.9)	0.458
Interval from symptom onset to admission	3.0 ± 1.5	5.4 ± 3.1	0.001
Initial laboratory tests:			
WBC count (/μL)	4186.8 ± 2320.1	3857.4 ± 2331.3	0.540
Leukopenia (<4000/μL)	33 (53.2)	18 (66.7)	0.239
Lymphocyte count (/μL)	800.0 ± 346.5	706.4 ± 325.2	0.242
Lymphopenia (<1500/μL)	59 (95.2)	26 (100)	0.552
Monocyte count (/μL)	214.1 ± 149.2	147.5 ± 125.9	0.049
Monocytopenia (<150/μL)	29 (46.8)	18 (69.2)	0.054
Platelet count (x10³/μL)	116.5 ± 52.6	112.4 ± 43.9	0.722
Thrombocytopenia (<150 × 10³/μL)	49 (79.0)	23 (85.2)	0.497
C-reactive protein (mg/dL)	11.7 ± 5.3	10.7 ± 5.7	0.457
Pneumonia severity on admission:			
PaO_2/FiO_2 ratio (mmHg)	295.4 ± 71.0	233.0 ± 80.79	<0.001
Hypoxaemia[a]	21 (33.9)	20 (74.1)	<0.001
Confusion	2 (3.2)	2 (7.4)	0.582
Tachypnoea (RR ≥ 30)	13 (21.0)	10 (37.0)	0.111
Shock (SBP <90 or DBP ≤60 mmHg)	40 (64.5)	14 (51.9)	0.261
CURB-65 (median, IQR)[b]	1 (0−1)	1 (1−1)	0.549
Radiological finding			
Multilobar involvement	31 (50.0)	18 (66.7)	0.146
Whole lung involvement	8 (12.9)	11 (40.7)	0.003
Pleural effusion	44 (71.0)	22 (81.5)	0.298
Microbiological test results:			
Co-detection of other respiratory viruses	5 (8.1)	2 (7.4)	1.000
Rhinovirus	2 (3.2)	1 (3.7)	1.000
Respiratory syncytial virus B	1 (1.6)	1 (3.7)	0.517
Influenza A[c]	1 (1.6)	0 (0.0)	1.000
Coronavirus OC43	1 (1.6)	0 (0.0)	1.000
Detection of bacterial pathogens	0 (0.0)	0 (0.0)	NA

Data are expressed as the number (%) of patients or mean ± SD unless indicated otherwise. Only one patient in the delayed treatment group had underlying asthma, while others had no comorbidities. One patient in the delayed treatment group had no data for differential count.

HAdV, human adenovirus; MMRC, modified Medical Research Council; WBC, white blood cell; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen ratio; SpO_2, peripheral capillary oxygen saturation; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; IQR, interquartile range; SD, standard deviation; BUN, blood urea nitrogen; NA, not applicable.

[a] PaO_2 <60 mmHg or SpO_2 <90%.
[b] Calculating CURB-65, no one met the criteria for elevated BUN or old age.
[c] The patient detected with influenza A received oseltamivir treatment.

group (6/27, 22.2% versus 3/62, 4.8%; p 0.020). Death occurred in one patient in the delayed treatment group.

Cidofovir was administered at around the recommended dosage of 5 mg/kg. Under-dosing was observed in 32.6% of patients (29/89) and did not differ between the two groups. Time intervals from admission to treatment and from symptom onset to treatment were significantly shorter in the early treatment group (both p < 0.001). Only 8.1% of the early treatment group (5/62) were treated with a second dose of cidofovir, while 40.7% of the delayed treatment group (11/27) were repeatedly treated (p = 0.001). Only one patient in the early treatment group experienced acute kidney injury (AKI) within 2 weeks of cidofovir treatment; the patient recovered thereafter. Two patients received CRRT support that was not associated with cidofovir treatment (Table 2, footnote).

Analyses for 21-day probability of respiratory failure

The clinical courses of the early and delayed treatment groups are depicted in Supplementary material Fig. S1. Early treatment was significantly associated with a lower hazard of respiratory failure progression (Supplementary material Fig. S2, p < 0.001). Univariate analysis for 21-day probability of respiratory failure is presented in Supplementary material Table S1. Among statistically significant factors, monocyte count, hypoxaemia, confusion, and whole lung

involvement were included in the multivariate analysis to adjust cidofovir treatment within 7 days after symptom onset (all p < 0.05). Detailed reasons for variable selection are presented in Table 3 (footnote). In the multivariate analyses, monocyte count (HR 0.995, 95%CI 0.991−1.000, p 0.042), confusion (HR 4.964, 95%CI 1.189−20.721, p 0.028), and cidofovir treatment within 7 days from symptom onset (HR 0.319, 95%CI 0.115−0.883, p = 0.028) were statistically significant (Table 3).

Discussion

Fatal HAdV pneumonia in adults has been reported, but an effective treatment modality has not been well evaluated [13,22]. Among currently available antiviral agents, cidofovir—a cytosine nucleotide analogue inhibiting DNA polymerase—is recommended for the treatment of severe HAdV infections based on *in vitro* and case reports [14,16,22,23]. However, it is not approved for HAdV treatment because of lack of clinical trials. In addition, its high cost and potential adverse effects hinder general use of the drug [22]. Since winter 2014, the Korean military has experienced an explosion of cases of severe HAdV pneumonia due to the ongoing outbreak of HAdV-55 and tried cidofovir for potentially severe HAdV pneumonia patients based on previous experience [6,13,17,18]. Since we treated most potentially severe HAdV cases

Table 2
Treatment and outcomes of cidofovir-treated patients with human adenovirus (HAdV) pneumonia

Variables	Early treatment, within 7 days from symptom onset (*n* = 62)	Delayed treatment, after 7 days from symptom onset (*n* = 27)	P value
Cidofovir treatment:			
Dosage (mg/kg)	5.0 ± 0.4	5.2 ± 0.5	0.095
Under-dosing (<5 mg/kg)	21 (33.9)	8 (29.6)	0.695
Interval from symptom onset to Tx, days	5.6 ± 1.4	10.0 ± 2.2	<0.001
Interval from admission to Tx, days	2.6 ± 1.5	4.6 ± 2.5	0.001
Repeated treatment (≥2 doses, weekly)	5 (8.1)	11 (40.7)	0.001
2 doses	4 (6.5)	10 (37.0)	NA
3 doses	0 (0.0)	1 (3.7)	NA
4 doses	1 (1.6)	0 (0.0)	NA
Initial antibiotics and other modalities:			
β-Lactams	61 (98.4)	27 (100)	1.000
Macrolides	33 (53.2)	16 (59.3)	0.599
Fluoroquinolones	49 (79.0)	21 (77.8)	0.894
Intravenous immunoglobulin	6 (9.7)	7 (25.9)	0.057
Outcome measures:			
Respiratory failure within 21 days after symptom onset	8 (12.9)	18 (66.7)	<0.001
Interval from symptom onset (median, range)	7.0 (6.0−10.0)	9.5 (5.0−16.0)	0.030
After 7 days from symptom onset	3/8 (37.5)	16/18 (88.9)	0.014
Interval from admission (median, range)	3.5 (1.0−5.0)	4.0 (1.0−10.0)	0.461
Hospital stay, days	22.0 ± 22.5	34.9 ± 19.5	0.012
ICU care	60 (96.8)	25 (92.6)	0.582
ICU stay, days	5.8 ± 5.9	10.3 ± 7.2	0.008
CRRT support[a]	1 (1.6)	1 (3.7)	0.517
ECMO support	3 (4.8)	6 (22.2)	0.020
Death	0 (0.0)	1 (3.7)	0.303
Subgroup analysis: among patients received cidofovir before respiratory failure:[b]			
Respiratory failure within 21 days after symptom onset	4/58 (6.9)	4/13 (30.8)	0.033
Interval from symptom onset (median, range)	9.5 (6.8−10.0)	10.0 (9.0−11.8)	0.486
After 7 days from symptom onset	3/4 (75.0)	4/4 (100)	1.000
Interval from admission (median, range)	3.5 (2.3−4.8)	5.0 (1.8−9.0)	0.486
Hospital stay, days	19.0 ± 16.2	32.0 ± 16.3	0.011
ICU care	56/58 (96.6)	11/13 (84.6)	0.151
ICU stay, days	5.2 ± 5.4	6.1 ± 4.8	0.607
CRRT support[b]	1/58 (1.7)	0/13 (0.0)	1.000
ECMO support	1/58 (1.7)	0/13 (0.0)	1.000
Death	0/58 (0.0)	0/13 (0.0)	NA

Data are expressed as the number (%) of patients or mean ± SD unless indicated otherwise.
Tx, treatment; ICU, intensive care unit; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; NA, not applicable.
[a] Although one of each group received CRRT support, one in the delayed treatment group experienced renal impairment before cidofovir administration and the other in the early treatment group experienced after 2 weeks of cidofovir treatment. Both of them recovered from the renal injury and did not require maintenance haemodialysis.
[b] The 21-day probability of respiratory failure was also significantly lower in the early treatment group of the subgroup (p 0.017 by log-rank test). Multivariate analysis was not conducted in the subgroup due to limited number of patients.

Table 3
Multivariate analysis for 21-day probability of respiratory failure in cidofovir-treated patients with human adenovirus (HAdV) pneumonia

Factors for respiratory failure	Multivariate analysis	
	HR (95%CI)	p value
Monocyte count	0.995 (0.991–1.000)	0.042
Hypoxaemia	1.876 (0.681–5.168)	0.224
Confusion	4.964 (1.189–20.721)	0.028
Whole lung involvement	1.343 (0.473–3.815)	0.580
Cidofovir treatment within 7 days after symptom onset	0.319 (0.115–0.883)	0.028

Among factors significant in the univariate analysis, monocyte count, hypoxaemia, confusion, whole lung involvement, and cidofovir treatment within 7 days after symptom onset were included in the multivariate analysis. Lymphocyte count was not included in the multivariate analysis since it showed colinearity with monocyte count which showed a stronger HR. PaO_2/FiO_2 ratio (partial pressure of arterial oxygen/fraction of inspired oxygen) and tachypnoea were not included in the multivariate analysis because they shared parameters or associated with hypoxaemia which showed the highest HR among these factors. CURB-65 was not included since confusion, which is a component of the CURB-65, showed a higher HR than CURB-65. Time intervals between symptom onset, admission, and cidofovir treatment were not included because they shared values with cidofovir treatment within 7 days after symptom onset, which is the main exposure of the cohort. Admission time from symptom onset was associated with cidofovir administration time because if the patient admitted to the military hospital early, the patient would have a higher chance of receiving cidofovir early. These two variables showed statistically significant linear association.

with cidofovir after the outbreak, a comparison between treated and non-treated patients was not feasible. However, we observed that early administration of cidofovir might prevent progression to respiratory failure and therefore designed the present retrospective cohort study comparing administration time of cidofovir. To our knowledge, the present study is the first comparative study to evaluate the effect of cidofovir for HAdV pneumonia, and could provide supporting data for further clinical studies.

Of note, the early treatment group within 7 days from symptom onset was significantly associated with a lower probability of respiratory failure, and late progression to respiratory failure after 10 days from symptom onset was not observed in this group. The treatment interval of 7 days from symptom onset dividing the early and delayed treatment groups was statistically significant in the multivariate analysis. These findings suggest clinical effectiveness of early cidofovir treatment for HAdV pneumonia. The importance of early treatment of respiratory viruses has been emphasized in studies assessing aerosolized ribavirin for respiratory syncytial virus [24], neuraminidase inhibitors for influenza [25], and convalescent plasma infusion therapy for severe acute respiratory syndrome (SARS) and severe influenza [26]. Likewise, cidofovir would be effective for treating HAdV pneumonia when administered early in the course of the disease, possibly before the progression to respiratory failure. Since cidofovir is expensive and approved only for the treatment of cytomegalovirus infection, it is not readily available in most settings, especially in resource-limited countries. In South Korea, patients need to purchase cidofovir individually through the Korea Orphan and Essential Drug Centre, and the process delays cidofovir administration by at least 1 day. For timely treatment of patients with potentially severe HAdV pneumonia and for further evaluation of clinical efficacy, easy access to cidofovir should be provided.

Although we could not assess patients with severe HAdV pneumonia who were not treated, outcome data can be compared with the previous report of the pre-cidofovir period of the Korean military (2011–2012) [11]. In that report, 12.2% of patients (6/49) with mild and severe HAdV infections progressed to respiratory failure and 6.1% of them (3/49) died. These outcomes would be worse than those of the early treatment group of the present study, with 12.9% (8/62) experiencing respiratory failure and no deaths among patients with potentially severe disease. Although direct comparison with the same severity criteria was not feasible, case fatality rate might have decreased after the introduction of cidofovir in the Korean military.

The present study findings should be interpreted carefully. First, our study does not imply effectiveness of cidofovir administered after progression to respiratory failure. Although this was not included in the scope of present study, we tested several statistical analyses among patients progressed to respiratory failure but could not find any meaningful association between the outcome and timing of cidofovir administration. Patients progressing to respiratory failure should be evaluated in another larger cohort containing both cidofovir-treated and non-treated patients. Second, the study population included young military personnel with minimal comorbidities. This cohort may demonstrate better outcomes and fewer complications than the general population. On the other hand, the study cohort was very homogeneous in terms of age and underlying conditions. Third, previously identified risk factors for respiratory failure—including hypoxaemia, multilobar involvement and pleural effusion—were not statistically significant in the multivariate analysis in the present study. This would be because these factors were used as inclusion criteria to select potentially severe patients. The purpose of the study was to evaluate the effect of cidofovir in the population at risk, not among all patients with HAdV pneumonia. Risk factors for respiratory failure were included in the multivariate analysis to adjust the effect of cidofovir treatment, and statistical non-significance does not necessarily mean that these factors were not associated with pneumonia progression. Fourth, as a retrospective study, there were significant differences between the early and delayed treatment group in terms of severity factors including hypoxaemia and whole lung involvement. Although these factors were adjusted in the multivariate analysis, interpretation of the study results should be cautious. Lastly, HAdV typing was not performed in all included patients. Although the major HAdV type during the study period was type 55 [6,13,17], other types of HAdV might have been included in the study cohort. Since *in vitro* data on cidofovir activity against various HAdV types are limited [14,27,28], careful interpretation of the study result is required, and further studies evaluating the effect of cidofovir on various HAdV types need to be conducted.

In conclusion, in this retrospective cohort study evaluating 89 cidofovir-treated HAdV pneumonia patients at risk for respiratory failure, early administration of cidofovir was associated with a lower hazard of progression to respiratory failure. It is suggested that cidofovir be administered within 7 days after symptom onset to prevent respiratory failure in patients with potentially severe HAdV pneumonia.

Transparency declarations

Author contributions

J.-H.K. and J.U.L. contributed equally to this paper.Appendix A. Supplementary dataThe following is the Supplementary data to this article:Multimedia component 1.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.10.012.

References

[1] Kim JM, Jung HD, Cheong HM, Lee A, Lee NJ, Chu H, et al. Nationwide surveillance of human acute respiratory virus infections between 2013 and 2015 in Korea. J Med Virol 2018;90:1177–83.

[2] Hakim FA, Tleyjeh IM. Severe adenovirus pneumonia in immunocompetent adults: a case report and review of the literature. Eur J Clin Microbiol Infect Dis 2008;27:153–8.

[3] Ryan MA, Gray GC, Smith B, McKeehan JA, Hawksworth AW, Malasig MD. Large epidemic of respiratory illness due to adenovirus types 7 and 3 in healthy young adults. Clin Infect Dis 2002;34:577–82.

[4] Top Jr FH, Dudding BA, Russell PK, Buescher EL. Control of respiratory disease in recruits with types 4 and 7 adenovirus vaccines. Am J Epidemiol 1971;94: 142–6.

[5] Hoke Jr CH, Snyder Jr CE. History of the restoration of adenovirus type 4 and type 7 vaccine, live oral (Adenovirus Vaccine) in the context of the Department of Defense acquisition system. Vaccine 2013;31:1623–32.

[6] Yoo H, Gu SH, Jung J, Song DH, Yoon C, Hong DJ, et al. Febrile respiratory illness associated with human adenovirus type 55 in South Korea military, 2014–2016. Emerg Infect Dis 2017;23:1016–20.

[7] Cao B, Huang GH, Pu ZH, Qu JX, Yu XM, Zhu Z, et al. Emergence of community-acquired adenovirus type 55 as a cause of community-onset pneumonia. Chest 2014;145:79–86.

[8] Lu QB, Tong YG, Wo Y, Wang HY, Liu EM, Gray GC, et al. Epidemiology of human adenovirus and molecular characterization of human adenovirus 55 in China, 2009–2012. Influenza Other Respir Virus. 2014;8:302–8.

[9] Walsh MP, Seto J, Jones MS, Chodosh J, Xu W, Seto D. Computational analysis identifies human adenovirus type 55 as a re-emergent acute respiratory disease pathogen. J Clin Microbiol 2010;48:991–3.

[10] Zhu Z, Zhang Y, Xu S, Yu P, Tian X, Wang L, et al. Outbreak of acute respiratory disease in China caused by B2 species of adenovirus type 11. J Clin Microbiol 2009;47:697–703.

[11] Heo JY, Lee JE, Kim HK, Choe KW. Acute lower respiratory tract infections in soldiers, South Korea, April 2011–March 2012. Emerg Infect Dis 2014;20: 875–7.

[12] Heo JY, Noh JY, Jeong HW, Choe KW, Song JY, Kim WJ, et al. Molecular epidemiology of human adenovirus-associated febrile respiratory illness in soldiers, South Korea (1). Emerg Infect Dis 2018;24:1221–7.

[13] Ko JH, Woo HT, Oh HS, Moon SM, Choi JY, Lim JU, et al. Ongoing outbreak of human adenovirus-associated acute respiratory illness in the Republic of Korea military, 2013 to 2018. Korean J Intern Med 2019. https://doi.org/10.3904/kjim.2019.092 [Epub ahead of print].

[14] Chemaly RF, Hill JA, Voigt S, Peggs KS. In vitro comparison of currently available and investigational antiviral agents against pathogenic human double-stranded DNA viruses: a systematic literature review. Antivir Res 2019;163:50–8.

[15] Doan ML, Mallory GB, Kaplan SL, Dishop MK, Schecter MG, McKenzie ED, et al. Treatment of adenovirus pneumonia with cidofovir in pediatric lung transplant recipients. J Heart Lung Transplant 2007;26:883–9.

[16] Bordigoni P, Carret AS, Venard V, Witz F, Le Faou A. Treatment of adenovirus infections in patients undergoing allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 2001;32:1290–7.

[17] Kim SJ, Kim K, Park SB, Hong DJ, Jhun BW. Outcomes of early administration of cidofovir in non-immunocompromised patients with severe adenovirus pneumonia. PLoS One 2015;10:e0122642.

[18] Yoon H, Jhun BW, Kim SJ, Kim K. Clinical characteristics and factors predicting respiratory failure in adenovirus pneumonia. Respirology 2016;21: 1243–50.

[19] Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003;58:377–82.

[20] Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988;93:580–6.

[21] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204–12.

[22] Lynch 3rd JP, Kajon AE. Adenovirus: epidemiology, global spread of novel serotypes, and advances in treatment and prevention. Semin Respir Crit Care Med 2016;37:586–602.

[23] Naesens L, Lenaerts L, Andrei G, Snoeck R, Van Beers D, Holy A, et al. Anti-adenovirus activities of several classes of nucleoside and nucleotide analogues. Antimicrob Agents Chemother 2005;49:1010–6.

[24] Shah DP, Ghantoji SS, Shah JN, El Taoum KK, Jiang Y, Popat U, et al. Impact of aerosolized ribavirin on mortality in 280 allogeneic haematopoietic stem cell transplant recipients with respiratory syncytial virus infections. J Antimicrob Chemother 2013;68:1872–80.

[25] Boikos C, Caya C, Doll MK, Kraicer-Melamed H, Dolph M, Delisle G, et al. Safety and effectiveness of neuraminidase inhibitors in situations of pandemic and/or novel/variant influenza: a systematic review of the literature, 2009—15. J Antimicrob Chemother 2017;72:1556–73.

[26] Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211:80–90.

[27] Gordon YJ, Araullo-Cruz TP, Johnson YF, Romanowski EG, Kinchington PR. Isolation of human adenovirus type 5 variants resistant to the antiviral cidofovir. Invest Ophthalmol Vis Sci 1996;37:2774–8.

[28] Hartline CB, Gustin KM, Wan WB, Ciesla SL, Beadle JR, Hostetler KY, et al. Ether lipid-ester prodrugs of acyclic nucleoside phosphonates: activity against adenovirus replication in vitro. J Infect Dis 2005;191:396–9.