Modern Rheumatology, **34**, 2024, 767–774
DOI: https://doi.org/10.1093/mr/road099
Advance access publication date: 6 October 2023
Original Article

Optimal dose of intravenous cyclophosphamide during remission induction therapy in ANCA-associated vasculitis: A retrospective cohort study of J-CANVAS

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Received 9 August 2023; Accepted 29 September 2023

ABSTRACT

Objectives: To identify the optimal dose of intravenous cyclophosphamide (IVCY) for induction therapy for anti-neutrophil cytoplasmic antibody-associated vasculitis.

Methods: We retrospectively assessed patients with antibody-associated vasculitis who received IVCY every 2–3 weeks during the remission induction phase. The associations of the IVCY dose with infection-free survival and relapse-free survival were analysed using a Cox regression model. We compared patients in three categories: very low-dose (VLD), low-dose (LD), and conventional dose (CD) (<7.5 mg/kg, 7.5–12.5 mg/kg, and >12.5 mg/kg, respectively). The non-linear association between IVCY dose and the outcomes was also evaluated.

Results: Of the 80 patients (median age 72 years), 12, 42, and 26 underwent the VLD, LD, and CD regimens, respectively, of whom 4, 3, and 7 developed infection or died. The adjusted hazard ratios for infection or death were 4.3 (95% confidence interval (CI) 0.94–19.8) for VLD and 5.1 (95% CI 1.21–21.3) for CD, compared with LD. We found the hazard ratio for infection or death increased when the initial IVCY dose exceeded 9 mg/kg. Relapse-free survival did not differ clearly.

Conclusion: Low-dose IVCY (7.5–12.5 mg/kg) may result in fewer infections and similar relapse rates compared with the conventional regimen (>12.5 mg/kg).

KEYWORDS: Antineutrophil cytoplasmic antibody-associated vasculitis; cyclophosphamide; intravenous cyclophosphamide; severe infection; restricted cubic spline

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic form of vasculitis that is characterized by the production of ANCA and can be categorized as microscopic polyangiitis (MPA), granulomatosis polyangiitis (GPA), or eosinophilic granulomatosis polyangiitis (EGPA) [1]. The current standard treatment is a combination of high-dose glucocorticoids and cyclophosphamide (CYC) or rituximab (RTX) [2], while the one-year mortality rate for patients with AAV is still high at 11–12% [3–5]. Treatment-related adverse events, such as infections, are the principal causes of death [6], and age and kidney function have been reported to be important predictors of this [3, 4].

Infection is a major adverse event associated with CYC, and it develops in a dose-dependent manner. The intravenous administration of CYC (IVCY) reduces the cumulative dose administered and the incidences of leukopenia and infections [7, 8], and therefore IVCY 15 mg/kg every 2–3 weeks (the CYCLOPS regimen) is widely used for remission induction therapy [7, 9–12]. In patients with systemic lupus erythematosus (SLE), low-dose IVCY (500 mg, six times) has been shown to be safer than high-dose IVCY (500 mg/m^2, eight times), with no difference in efficacy, which justifies the use of low-dose IVCY [13]. In addition, for patients with AAV, the coronavirus disease-19 pandemic has prompted the need to identify the IVCY dosing regimen that is optimal for remission induction and minimizes the risk of infection [14]. In the CORTAGE study, a fixed dose of IVCY of 500 mg every 2–3 weeks for six times was as effective as the conventional regimen of IVCY in patients aged ≥65 years, and was associated with a lower incidence of serious adverse events [15]. However, the 500 mg fixed dose regimen does not consider variations in patient size.

For the present study, we hypothesized that a body size-based low-dose IVCY regimen would be a preferable treatment to the conventional dose regimen, with fewer adverse events but similar effectiveness. Thus, we aimed to identify the optimal dose of IVCY in terms of both safety and effectiveness for remission induction therapy in patients with AAV.

Method

Study design and data source

We performed a multi-centre retrospective cohort study using data from the Japan Collaborative Registry of ANCA-associated Vasculitis (J-CANVAS), a nationwide registry established by 24 hospitals in Japan. This registry enrolled adult (≥20 years) patients with newly diagnosed or severe relapsing AAV between January 2017 and June 2020. The patients were classified as having MPA, GPA, or EGPA, according to the definitions of the 2012 International Chapel Hill Consensus Conference [1] and the European Medicines Agency algorithm [16]. The participants were followed from disease onset to death, loss to follow-up, or June 2021.

Data collection

Data regarding the background (age, sex, disease type [MPA, GPA, or EGPA], newly-diagnosed and relapsed, body mass, height, a history of smoking, and presence of comorbidities including chronic bronchitis/bronchiectasis, diabetes, chronic kidney disease, and heart disease) of the participants, laboratory data (serum creatinine concentration, estimated glomerular filtration rate [eGFR], IgG titre, blood cell counts [neutrophils, lymphocytes, platelets], haemoglobin concentration, ANCA serotype [MPO-ANCA or PR3-ANCA]), and details of organ involvements (Birmingham vasculitis activity score version 3 [BVAS] [17]) were extracted from the database. The therapeutic agents being administered (glucocorticoid dose [prednisone equivalent] during the first 48 weeks following the start of treatment, methylprednisolone pulse, RTX, CYC, mycophenolate mofetil, methotrexate, azathioprine, and mepolizumab, the initial and cumulative doses of IVCY and chemoprophylactic drugs against Pneumocystis jirovecii pneumonia (PCP) during the first 24 weeks following the start of treatment were also recorded. The outcomes recorded were severe infection (defined as 'infections requiring hospitalization or prolongation of existing hospitalization' [18]), relapse (defined as BVAS >0), adverse events (such as neutropenia [count <1500/μL], lymphopenia [count <800/μL], anaemia [haemoglobin concentration <10 mg/dL], thrombocytopenia [count <75,000/μL] [18], and hypogammaglobulinemia [concentration <600 mg/dL] [19]), and death following the start of treatment. The collected data were recorded and integrated using the electronic data collection system Viedoc (PCG solutions, Uppsala, Sweden).

Participants

The patients who were eligible for inclusion were those who had undergone IVCY therapy every 2–3 weeks (defined as 11–24 days, with a margin of 3 days) as remission induction therapy for AAV. Patients with an eGFR <15 ml/min/1.73 m^2

or who were undergoing haemodialysis, and those who were administered RTX or had an infection prior to the start of IVCY were excluded.

Exposure and outcomes

The initial dose of IVCY that was administered as remission induction therapy for AAV was used as the main exposure and was categorized as very low-dose (VLD, <7.5 mg/kg), low-dose (LD, 7.5–12.5 mg/kg), and conventional dose (CD, >12.5 mg/kg), based on the CYCLOPS regimen. The co-primary outcomes were infection-free survival (defined as time to severe infection or death from any cause) and relapse-free survival (defined as time to relapse or death from any cause) after the initiation of treatment.

The incidences of adverse events and reductions in glucocorticoid dose up to 48 weeks were also evaluated.

Statistical analysis

Data are summarized as the median (interquartile range [IQR]) or absolute numbers (percentages). Time-to-event data are described using Kaplan-Meier survival curves or cumulative incidence functions, with death as a competing risk. The associations of the initial dose of IVCY with infection-free survival and relapse-free survival were evaluated using Cox regression models. Potential confounding factors between IVCY dose and severe infection were prespecified based on previous studies [20–23] and clinical perspectives, and were structured using directed acyclic graph (DAG) (Supplementary Figure S1). Based on the DAG, multivariate analyses were performed by two models (adjusted for age, eGFR, BVAS, relapsed cases [model 1, representing a minimal sufficient adjustment set]; age, sex, disease type, ANCA type, relapsed cases, serum albumin concentration, a history of smoking, the presence of diabetes, the presence of chronic bronchitis/bronchiectasis, eGFR, BVAS, the initial glucocorticoid dose, and the use of a methylprednisolone pulse [model 2, representing an all-possible adjustment set]). The magnitude of the associations identified was described using hazard ratios (HRs) and 95% confidence intervals (CIs). We performed a sensitivity analysis: we divided the analysis into three groups to ensure equal numbers at IVCY mg/kg. In addition, non-linear dose–response associations were expressed by incorporating restricted cubic spline (RCS) functions with four knots at the 5th, 35th, 65th, and 95th percentiles of the initial IVCY dose into Cox regression models (adjusted with model 2). IVCY doses were expressed in three ways: mg/kg, mg/m^2, and the ratio to CYCLOPS regimen (actual IVCY dose/the recommended IVCY dose in the CYCLOPS regimen, which was based on the age and kidney function of the patient; Supplementary Table S1). Statistical analyses were performed using R software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics

The study complied with the principles of the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research of the Ministry of Health, Labour, and Welfare of Japan. Because of the retrospective nature of the study, the requirement for written informed consent was waived. We used only anonymized data and provided an opportunity for patients to opt-out of participation. The study was approved by the local Institutional Review Boards (IRBs) of the participating institutions, including the Ethics Committee of Kyoto Prefectural University of Medicine (approval number: ERB-C-1928).

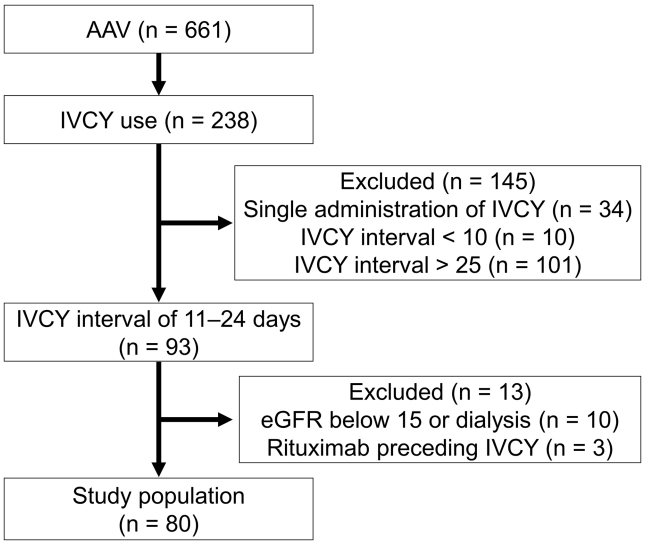

Figure 1. Flow diagram. eGFR, estimated glomerular filtration rate; IVCY, intravenous cyclophosphamide.

Results

Participant characteristics

Of the 661 Japanese AAV patients registered in J-CANVAS, 238 were treated with IVCY, of whom 93 underwent IVCY at intervals of 2–3 weeks. Ten patients with eGFRs <15 ml/min/1.73 m^2 or who were undergoing haemodialysis and three patients who were administered RTX prior to IVCY were excluded. Thus, data from 80 patients were analysed (Figure 1).

The baseline data for the participants (43 with MPA, 16 with GPA, and 21 with EGPA; median age 72 years [IQR 66–76 years]; 53 women; median eGFR 65.7 mL/min/1.73 m^2 [IQR 42–86.2 mL/min/1.73 m^2]; median BVAS 16 [IQR 12–20]) are shown in Table 1. The median initial dose of IVCY was 10 mg/kg (IQR 8.2–13.7 mg/kg), and the VLD, LD, and CD groups comprised 12, 42, and 26 participants, respectively. Details of the IVCY dose in the participants are shown in Supplementary Table S2. The IVCY dosing intervals were comparable between the three groups and changes in the second dose did not occur in most patients. Other immunosuppressants besides IVCY and chemoprophylactic drugs against PCP are shown in Supplementary Table S3. The median follow-up period was 720 days [IQR 373–1138 days].

Association between the initial IVCY dose and severe infection

During the follow-up period, 13 of the participants (16.2%) had developed a severe infection, and the median time to onset of the first severe infection was 110 (IQR 93–256) days. Three (3.8%) participants died, but none of these deaths occurred because of apparent vasculitis or infection. The infection-free survival time for each IVCY dose group is shown in Figure 2a.

Table 1. Baseline characteristics and treatments of the participants.

	All participants	VLD (IVCY <7.5 mg/kg)	LD (IVCY 7.5–12.5 mg/kg)	CD (IVCY >12.5 mg/kg)
Number of participants	*n* = 80	*n* = 12	*n* = 42	*n* = 26
Age at diagnosis, years, median [IQR]	72 [66, 76]	73 [71, 81]	72 [65, 78]	70 [65, 74]
Women, *n* (%)	53 (66)	5 (42)	32 (76)	16 (62)
BMI, kg/m^2, median [IQR]	21.5 [19.1, 24.7]	21.8 [19.9, 25.1]	21.8 [20.2, 25.1]	20.3 [18.8, 23.9]
History of smoking, *n* (%)	32 (40)	6 (50)	15 (36)	11 (42)
Relapse cases, *n* (%)	5 (6)	1 (8)	2 (5)	2 (8)
AAV classification				
–GPA, *n* (%)	16 (20)	0 (0)	9 (21)	7 (27)
–MPA, *n* (%)	43 (54)	10 (83)	21 (50)	12 (46)
–EGPA, *n* (%)	21 (26)	2 (17)	12 (29)	7 (27)
Type of ANCA				
–PR3-ANCA, *n* (%)	8 (10)	0 (0)	4 (9.5)	4 (15)
–MPO-ANCA, *n* (%)	59 (74)	11 (92)	30 (71)	18 (69)
–Seronegative, *n* (%)	13 (16)	1 (8.3)	8 (19)	4 (15)
Organ involvement				
–Renal, *n* (%)	51 (63.7)	11 (92)	24 (57)	16 (61.5)
–Chest, *n* (%)	35 (43.8)	5 (42)	20 (48)	10 (38.5)
–Alveolar haemorrhage, *n* (%)	8 (10)	2 (17)	2 (5)	4 (15)
–Nervous, *n* (%)	38 (47.5)	4 (33)	24 (57)	10 (38.5)
AAV-specific indices				
–FFS at diagnosis, median [IQR]	1 [1, 2]	2 [1, 2]	1 [1, 2]	1 [1, 2]
–Mean BVAS at diagnosis, median [IQR]	16 [12, 20]	16 [12.8, 20.8]	16.5 [12.3, 20]	14 [11.3, 20]
Routine laboratory results at diagnosis				
–Serum albumin, g/dL, median [IQR]	2.8 [2.4, 3.1]	2.5 [2.2, 2.9]	2.8 [2.3, 3.1]	3 [2.5, 3.3]
–Serum creatinine, mg/dL, median [IQR]	0.76 [0.59, 1.2]	1. [1.01, 1.81]	0.73 [0.58, 1.18]	0.72 [0.55, 0.93]
–eGFR, median [IQR]	65.7 [42, 86.2]	43.8 [27.7, 53.7]	66.5 [41.9, 85.3]	72.1 [50.5, 92.9]
Comorbidities at diagnosis				
–Chronic bronchitis/bronchiectasis, *n* (%)	7 (8.8)	2 (17)	4 (9.5)	1 (3.8)
–Diabetes, *n* (%)	19 (24)	3 (25)	9 (21)	7 (27)
–Chronic kidney disease, *n* (%)	7 (8.8)	3 (25)	4 (9.5)	0 (0)
Glucocorticoid use				
–Initial dose (prednisone equivalent), mg/day, median [IQR]	50 [40, 60]	50 [49, 60]	50 [40, 60]	50 [40, 60]
–Methylprednisolone pulse, *n* (%)	41 (51)	6 (50)	24 (57)	11 (42)

Participants were categorized according to IVCY dose: very low-dose (VLD), low-dose (LD), and conventional dose (CD) (<7.5, 7.5–12.5, and >12.5 mg/kg, respectively). Continuous variables are described using the median (interquartile range, IQR), and categorical variables are described using numbers (percentages).
IVCY, intravenous cyclophosphamide; BMI, body mass index; AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; GPA, granulomatosis polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis polyangiitis; FFS, Five Factor Score; BVAS, Birmingham vasculitis activity score version 3; eGFR, estimated glomerular filtration rate.

The cumulative incidences of infection and death are shown in Supplementary Figure S2.

In the multivariate model 1, the HRs for severe infection or death were 4.3 (95% CI 0.94–19.8) for the VLD regimen and 5.1 (95% CI 1.23–21.3) for the CD regimen, compared with the LD regimen (Table 2). The results of other models are also included in Table 2.

Association between the initial IVCY dose and relapse

During the follow up period, seven participants (8.8%) relapsed, and the median time to relapse was 255 days (IQR 191–259 days). The relapse-free survival time for each IVCY dose group is shown in Figure 2b. The cumulative incidences of relapse are shown in Supplementary Figure S2. In the multivariate model 1, the HRs for relapse or death were 1.3 (95% CI 0.37–4.6) for the VLD regimen and 0.39 (95% CI 0.1–1.5) for the CD regimen, compared with the LD regimen (Table 3). The results of other models are also included in Table 3.

Sensitivity analysis

A sensitivity analysis was performed when the three groups were divided into equal numbers using the IVCY mg/kg tertile point instead of classification based on the CYCLOPS

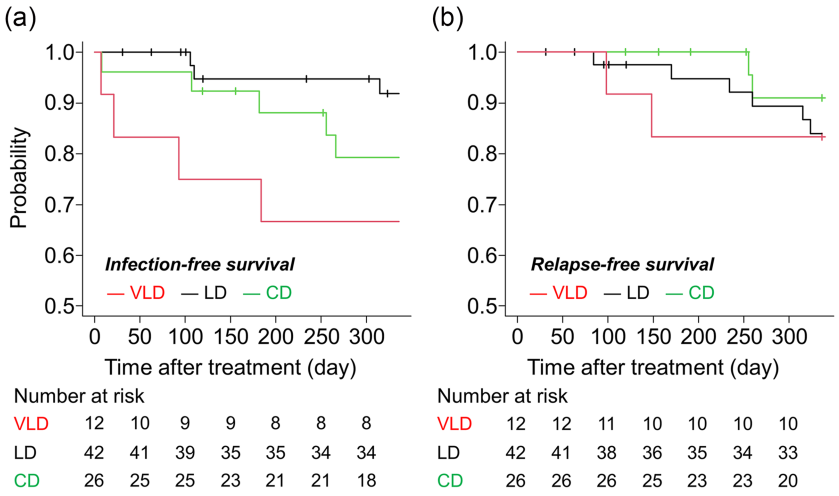

Figure 2. Associations between IVCY dose and clinical outcomes. (a) Infection-free survival after treatment initiation. (b) Relapse-free survival after treatment initiation. Participants were categorized according to IVCY dose: very low-dose (VLD), low-dose (LD), and conventional dose (CD) (<7.5, 7.5–12.5, and >12.5 mg/kg, respectively). IVCY, intravenous cyclophosphamide.

Table 2. Association between IVCY dose and infection-free survival.

	Hazard ratio for severe infection or death (95% CI), *P*-value		
	Univariate	Model 1 (main analysis)	Model 2
VLD (IVCY <7.5 mg/kg)	5.2 (1.2–23.2), 0.031	4.3 (0.94–19.8), 0.06	2.6 (0.32–21.8), 0.37
LD (IVCY 7.5–12.5 mg/kg)	Reference	Reference	Reference
CD (IVCY >12.5 mg/kg)	3.8 (0.98–14.6), 0.054	5.1 (1.21–21.3), 0.026	14.2 (2.1–94.8), 0.006

Participants were categorized according to IVCY dose: very low-dose (VLD), low-dose (LD), and conventional dose (CD) (<7.5, 7.5–12.5, and >12.5 mg/kg, respectively). Model 1 was adjusted for age, eGFR, BVAS, and relapsed cases (minimal sufficient adjustment set). Model 2 was adjusted for age, sex, disease type, ANCA type, relapsed cases, serum albumin concentration, a history of smoking, the presence of diabetes, the presence of chronic bronchitis/bronchiectasis, eGFR, BVAS, the initial glucocorticoid dose, and the use of a methylprednisolone pulse (all-possible adjustment set).
IVCY, intravenous cyclophosphamide; 95% CI, 95% confidence interval; ANCA, antineutrophil cytoplasmic antibody serotype; BVAS, Birmingham vasculitis activity score version 3; eGFR, estimated glomerular filtration rate.

regimen. There were 27 patients with tertile 1 (<8.8 mg/kg), 27 patients with tertile 2 (8.8–12.5 mg/kg), and 26 patients with tertile 3 (>12.5 mg/kg). In the multivariate models (same confounding factor adjustment as in Model 1), the HRs for severe infection or death were 2.4 (95% CI 0.45–12.5) for the tertile 1 and 5.8 (95% CI 1.1–30.6) for the tertile 3 compared with the tertile 2; the HRs for relapse or death were 0.9 (95% CI 0.28–2.9) for the tertile 1 and 0.41 (95% CI 0.1–1.7) for the tertile 3 compared with the tertile 2 (Supplementary Table S4).

Non-linear associations of the initial IVCY dose with severe infection and relapse

The RCS analysis revealed that the HR for severe infection or death increased when the initial IVCY dose exceeded 9 mg/kg (Figure 3a). For body surface area-based dosing, the risk of severe infection increased when the IVCY dose exceeded 350 mg/m^2 (Supplementary Figure S3). In addition, exceeding the recommended dose in the CYCLOPS regimen was associated with a higher risk of severe infection (Supplementary Figure S3).

For the association between the initial dose of IVCY and the risk of relapse, a nearly horizontal RCS curve was found (Figure 3b and Supplementary Figure S3).

Adverse events in each group

Cytopenia developed in 7 (58%) participants in the VLD group, 30 (71%) in the LD group, and 16 (62%) in the CD group up to 24 weeks after the initiation of treatment (Table 4).

The lowest median IgG titres up to 24 weeks after the initiation of treatment were 568.5 mg/dL (IQR 497.8–764.5 mg/dL) in the VLD group, 736 mg/dL (IQR 547–931 mg/dL) in the LD group, and 603 mg/dL (IQR 506.5–810.5 mg/dL) in the CD group. The incidences of hypogammaglobulinemia in each group are shown in Table 4.

Reductions in glucocorticoid dose in each group

The prednisone doses being administered at 48 weeks did not differ among the groups, with median values of 7 mg/day (IQR 4.5–11 mg/day) in the VLD group, 7.5 mg/day (IQR 5–10 mg/day) in the LD group, and 8 mg/day (IQR 7–11 mg/day) in the CD group (Supplementary Table S5).

Discussion

In the present study, we have investigated the association between the dose of IVCY and the risk of severe infection during remission induction therapy for AAV, using data from a nationwide registry in Japan. We have shown that the LD regimen (7.5–12.5 mg/kg) result in fewer severe infections compared with the CD regimen (>12.5 mg/kg), with comparable therapeutic effectiveness. There was no obvious difference between the CD and LD regimens with respect to the rate

Table 3. Association between IVCY dose and relapse-free survival.

	Hazard ratio for relapse or death (95% CI), *P*-value		
	Univariate	Model 1 (main analysis)	Model 2
VLD (IVCY <7.5 mg/kg)	1.3 (0.4–4.1), 0.67	1.3 (0.37–4.6), 0.68	1 (0.22–4.8), 0.98
LD (IVCY 7.5–12.5 mg/kg)	Reference	Reference	Reference
CD (IVCY >12.5 mg/kg)	0.47 (0.13–1.7), 0.25	0.39 (0.1–1.5), 0.18	0.44 (0.08–2.4), 0.34

Participants were categorized according to IVCY dose: very low-dose (VLD), low-dose (LD), and conventional dose (CD) (<7.5, 7.5–12.5, and >12.5 mg/kg, respectively). Model 1 was adjusted for age, eGFR, BVAS, and relapsed cases (minimal sufficient adjustment set). Model 2 was adjusted for age, sex, disease type, ANCA type, relapsed cases, serum albumin concentration, a history of smoking, the presence of diabetes, the presence of chronic bronchitis/bronchiectasis, eGFR, BVAS, the initial glucocorticoid dose, and the use of a methylprednisolone pulse (all-possible adjustment set).
IVCY, intravenous cyclophosphamide; 95% CI, 95% confidence interval; ANCA, antineutrophil cytoplasmic antibody serotype; BVAS, Birmingham vasculitis activity score version 3; eGFR, estimated glomerular filtration rate.

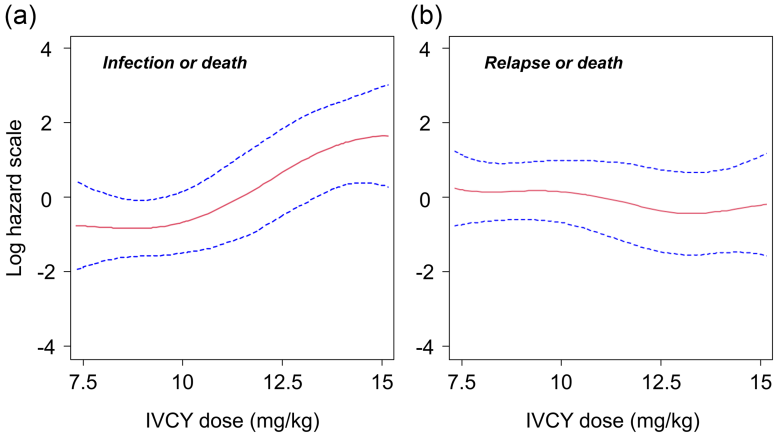

Figure 3. Non-linear association between IVCY dose and clinical outcomes. (a) IVCY dose (mg/kg) vs. infection-free survival. (b) IVCY dose (mg/kg) vs. relapse-free survival. The log hazard ratio (solid red line) and 95% confidence intervals (dashed blue lines) were estimated using Cox models with restricted cubic spline (four knots). Adjusted variables were age, sex, disease type, ANCA type, relapsed cases, serum albumin concentration, a history of smoking, the presence of diabetes, the presence of chronicbronchitis/bronchiectasis, eGFR, BVAS, the initial glucocorticoid dose, and the use of a methylprednisolone pulse. ANCA, antineutrophil cytoplasmic antibody serotype; eGFR, estimated glomerular filtration rate; IVCY, intravenous cyclophosphamide.

of glucocorticoid dose reduction or the severity of cytopenias, but the decrease in IgG titers was smaller in the LD regimen than in the CD regimen. Furthermore, RCS regression revealed a non-linear association between IVCY dose and severe infection, and the HR for severe infection or death increased when the initial IVCY dose exceeded 9 mg/kg (or ∼350 mg/m^2). These findings can help clinicians optimize the dosage of IVCY for patients.

Regimens that adjust CYC dose according to the kidney function and age of the patient has been proposed and implemented in several previous trials. However, none of these have demonstrated that this approach is safer than the conventional full-dose regimen. In the CORTAGE study, a fixed low dose of 500 mg reduced the incidence of adverse events, independent of renal function, compared with the conventional regimen of 500 mg/m^2, and did not affect the remission rate. For the present study, we hypothesized that a low-dose regimen with further dosage adjustment on the basis of body size would be more appropriate. The IVCY doses proposed in the present study are also generally consistent with those used for SLE and systemic sclerosis (SSc). For example, a fixed low-dose IVCY regimen of 500 mg every 2 weeks in patients with lupus nephritis and 600 mg/m^2 once a month in those with SSc-associated interstitial lung disease have been used. These are equivalent to 300–450 mg/m^2 or 7.5–12.5 mg/kg at 2–3 week intervals [24]. Indeed, in the majority of our patients (69/80), the recommended IVCY dose in the CYCLOPS regimen based on age and kidney function fell between 7.5 mg/kg and 12.5 mg/kg.

The possible mechanisms underlying the association between IVCY dose and severe infection that we have demonstrated in the present study are as follows. The magnitude of the decrease in IgG was smaller under the LD regimen than under the CD regimen in the study. Higher incidences of infection have been reported in association with several diseases in patients with low IgG titres [25–27]. CYC has been reported to dose-dependently increase the risk of cytopenia, and this may also be linked to the risk of infection [28, 29]. By means of a RCS, we identified a non-linear association between the initial IVCY dose and the hazard ratio for severe infection or death, which increased when the initial IVCY dose exceeded 9 mg/kg. Highly active AAV has been reported to predict severe infection, and under-dosing with IVCY may increase the risks of infection and death, as a result of residual disease activity [30]. Although it was originally believed that 400–1000 mg/m^2 doses were required for effective chemotherapy and the induction of systemic immunosuppression, ≤300 mg/m^2 has also been reported to be sufficient for immunomodulation in humans [29]. These findings suggest that conventional doses of IVCY of 15 mg/kg or 500 mg/m^2 may be excessive for the immunomodulation of autoimmune diseases, such as vasculitis. Overall, IVCY

Table 4. Adverse events up to 24 weeks after the initiation of treatment.

	VLD (IVCY <7.5 mg/kg)	LD (IVCY 7.5–12.5 mg/kg)	CD (IVCY >12.5 mg/kg)
Number of participants	*n* = 12	*n* = 42	*n* = 26
Cytopenia, *n* (%)	7 (58)	30 (71)	16 (62)
Lymphopenia, *n* (%)	6 (50)	26 (62)	16 (62)
Neutropenia, *n* (%)	1 (8)	2 (5)	1 (4)
Anaemia, *n* (%)	4 (33)	16 (38)	10 (39)
Thrombocytopenia, *n* (%)	1 (8)	3 (7)	2 (8)
Hypogammaglobulinemia, *n* (%)	5 (50)	12 (32)	12 (50)
Severe infection, *n* (%)	3 (25)	2 (5)	2 (8)
Death, *n* (%)	1 (8)	0 (0)	0 (0)

n (%) represents the number and percentage of patients. Participants were categorized according to IVCY dose: very low-dose (VLD), low-dose (LD), and conventional dose (CD) (<7.5, 7.5–12.5, and >12.5 mg/kg, respectively). 'Cytopenia' included lymphopenia, neutropenia, anaemia, and thrombocytopenia. Lymphopenia: <800/μL, neutropenia: <1500/μL, anaemia: <10 mg/dL, thrombocytopenia: <75,000/m^3, hypogammaglobulinemia: minimum serum IgG titre <600 mg/dL up to 24 weeks after the start of treatment.
IVCY, intravenous cyclophosphamide.

dose should be neither too high nor too low, and a low-dose regimen of 7.5–12.5 mg/kg (approximately 9 mg/kg or ∼350 mg/m^2) may be associated with an optimal balance between efficacy and safety. Further research is needed on IVCY dosing, including randomized controlled trials.

The principal strength of the present study was that we used a nationwide, multi-centre study in Japan to characterize the optimal IVCY dosage for remission induction therapy in patients with AAV. Furthermore, patients were approximately 10 years older than patients studied in most major AAV trials. Patients may have received the VLD regimen, which was below the minimum dose recommended by the CYCLOPS regimen, because they had a poorer performance status. However, although the crude incidence of severe infections was higher in the VLD group, there was no clear difference between the VLD and LD groups after adjustment for confounding factors. By dividing IVCY doses into three categories without excluding outliers such as VLD, this study focused on comparing CD and LD regimens within the CYCLOPS regimen, and was also able to assess dose-response by RCS.

The study also had some limitations that are inherent to observational studies of real-life clinical practice. First, the sample size may not have been sufficient and there is uncertainty in our findings. Second, no strict treatment protocol was set, and therefore the treatment regimens varied between hospitals and physicians; variations in IVCY doses and intervals, as well as differences in treatment other than IVCY, could have affected the estimated risk of severe infection. Particularly, there could be an effect of time-dependent confounding related to the treatment performed after the IVCY. However, there does not seem to be a clear difference in the immunosuppressive drugs and glucocorticoid dose reduction between the LD and CD groups. To address inconsistencies in the intervention, by limiting the administration to 2–3 weeks intervals, we were able to determine how the various IVCY doses relate to the risk of severe infection. Third, patients who could not receive a second or subsequent administration of IVCY were not included in the analysis, which may have led to an underestimation of the incidence of severe infection. Finally, as the effectiveness of IVCY varies with ethnicity [31], further studies including non-Asians are needed.

Conclusion

In the present study, we have identified an optimal low-dose IVCY regimen for remission induction therapy in patients with AAV, which is expected to improve the prognosis of AAV. IVCY doses of 7.5–12.5 mg/kg (approximately 9 mg/kg), compared with the conventional dose of 15 mg/kg, may reduce the risk of infection while maintaining similar effectiveness.

Acknowledgements

We thank Mark Cleasby, PhD from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript. This work was supported by J-STAR-CR, the Committee on Clinical Research, Japan College of Rheumatology. Statistical advice was obtained from Hisashi Noma. This work was presented as a workshop at the 67th Annual Scientific Meeting of the Japan College of Rheumatology.

Supplementary data

Supplementary data is available at *Modern Rheumatology* online.

Conflict of interest

T.Ki. has received honoraria for speaker's bureaus from Asahi Kasei Pharma and Chugai. S.O. has received honoraria for speaker's bureaus from Asahi Kasei Pharma. D.N. has received scholarship grants from Asahi Kasei Pharma, Chugai, and honoraria for speaker's bureaus from Asahi Kasei Pharma, Chugai. N.T. has received honoraria for speaker's bureaus from Asahi Kasei Pharma, Chugai, Kyowa Kirin, Mylan, Pfizer and Towa Pharmaceutical. A.N. has received honoraria for speaker's bureaus from Asahi Kasei Pharma and Chugai. S.H. has received research grants from Asahi Kasei Pharma, Chugai, Pfizer and Shionogi, and honoraria for speaker's bureaus from Asahi Kasei Pharma, Chugai, Kyorin and Pfizer. K.M. has received research grants from Asahi Kasei Pharma and Chugai. M.Kat. has received honoraria for speaker's bureaus from Asahi Kasei Pharma, Chugai, Kyowa Kirin, Pfizer and Viatris. T.Taka. has received scholarship grants from Chugai and, Kyowa Kirin and honoraria for speaker's bureaus from Chugai. W.F. has received honoraria for speaker's bureaus from Asahi Kasei Pharma, Chugai, Pfizer and Takeda. M.Koh. has received honoraria for speaker's bureaus from Asahi Kasei Pharma, Chugai and Pfizer. Y.Ka. has received research grants from Asahi Kasei Pharma and Chugai, and honoraria for speaker's bureaus from Asahi Kasei Pharma, Chugai Pharmaceutical and Mylan. The other authors declare that they have no conflicts of interest to disclose.

Funding

This work was supported by the Japan Society for the Promotion of Science KAKENHI [grant number JP22K16348].

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Contributors

H.S., T.Ki., A.H., T.Iha., N.Y., T.Ka., and Y.Ka. contributed to the study conception and design. S.O., M.Kad., D.N., Y.A., N.T., A.N., Y.K., N.K., Y.Y., T.Y., K.E., S.H., K.M., T.Take., K.I., M.Kat., R.Y., Y.Ma., Y.S., R.N., R.O., T.Taka., T.Ito., M.M., A.T., and Y.Mi. contributed to the acquisition of data. H.S., T.Ki., K.F., W.F., T.S., M.W., M.Koh., and Y.Ka. performed data analysis and interpretation. H.S. and T.Ki. drafted the manuscript. All authors revised and approved the final version to be published. Y.Ka. is responsible for the overall content as guarantor.

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