Intravenous Vitamin D Receptor Activators in Dialysis Introduction Period

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Abstract

Background Usage of vitamin D receptor activator (VDRA) for chronic kidney disease (CKD) including patients on dialysis patients has been controversial yet. It is unknown when to begin or discontinue VDRA therapy, the type of VDRA to administer, and the method of delivery, intravenous or oral for survival in CKD patients. Therefore, we examined whether intravenous or oral VDRA early after dialysis initiation affected mortality in incident dialysis patients.

Methods The study database was derived from the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP), a multicenter, prospective, cohort analysis of 1,520 consecutive patients who began dialysis at the 17 AICOPP group centers between October 2011 and September 2013. We excluded the 262 patients who died by March 2015, 15 patients were lost to follow-up, 241 patients with unconfirmed information about use of VDRA in March 2015, and 35 patients who discontinued VDRA between dialysis initiation and March 2015. Finally, 967 patients participated in the present study. We classified the participating patients into three groups according to the usage of VDRA in March 2015: no use of VDRA (NV group), oral VDRA (OV group), and intravenous VDRA (IV group) and compared their all-cause mortality.

Results There were 104 deaths during the follow-up period (NV group, 27 cases; OV group, 53 cases; IV group, 24 cases). Significant differences between the cumulative survival rates were observed for the three groups ($p = 0.010$). The IV group was associated with low all-cause mortality compared to the NV group (Hazard ratio = 0.46, 95% CI = 0.24–0.89, $p = 0.020$) by multivariate Cox proportional hazard analysis using the stepwise method.

Conclusions Our study shows that early introduction of intravenous VDRA to patients on hemodialysis seems to be associated with better prognosis.

Trial Registration The trial registration no. is UMIN 000007096, registered on January 18, 2012. 298words, Text: 2967 words

Background

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is one of the most important complications in patients on dialysis because it is closely associated with mortality. The treatment strategy for CKD-MBD includes dietary phosphorus restriction, phosphate binders, vitamin D receptor activators (VDRA), and calcimimetics. Among them, VDRA plays a central role as medication for CKD-MBD. Many reports have shown vitamin D status is related to survival and native vitamin D supplementation or administration of VDRA was related to better prognosis [1–5]. The beneficial results were considered to be derived from pleiotropic actions for left ventricular hypertrophy [6–9], insulin resistance [10], and the immune system [11]. On the other hand, it is possible that VDRA leads to ectopic calcification, especially vascular calcification through hypercalcemia and hyperphosphatemia [12]. Thus, use of VDRA for CKD patients has been controversial yet.

According to Clinical practice guidelines for the management of CKD-MBD by the Japanese Society for Dialysis Therapy, dietary phosphorus restriction, the use of a calcium-containing phosphorus binder, and/or the administration of oral VDRA are recommended to control parathyroid hormone (PTH) levels in pre-dialysis. In addition, medical therapy, including serum phosphorus/calcium management and VDRA and/or cinacalcet hydrochloride are recommended to decrease the level of intact PTH[13]. Recently, Kidney Disease Improving Global Outcomes (KDIGO) 2017 Clinical Practice guidelines suggested that calcitriol and vitamin D analogs should not be used routinely for adult patients with CKD G3a–G5 not on dialysis and it is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4–G5 with severe and progressive hyperparathyroidism [14]. Use of VDRA for CKD patients has been controversial yet.

The serum calcitriol level decreases in the early CKD stage and is under the lower normal limit at dialysis initiation in most CKD patients [15]. In addition, vitamin D status represented by 25-hydroxyvitamin D levels is associated with pleiotropic actions in an autocrine or paracrine manner after activation to calcitriol [16]. Therefore, it would be necessary to supply native vitamin D or administer VDRA for CKD patients. However, it is unknown when to start or discontinue VDRA therapy, the type of VDRA to administer, and the method of delivery (intravenous or oral) for survival of CKD patients. Therefore, we examined the association between the timing of VDRA therapy initiation and mortality in incident dialysis patients. Moreover, we compared all-cause mortality between the three groups (no use of VDRA, oral VDRA, and intravenous VDRA).

Methods

Subjects

The study database was derived from the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP), a multicenter, prospective, cohort analysis of 1,520 consecutive patients who began dialysis at the 17 AICOPP group centers between October 2011 and September 2013 [17]. This study was registered as UMIN000007096. Figure 1 shows patient flow. We excluded the 262 patients who died by March 2015, 15 patients lost to follow-up, 241 patients with unconfirmed information about use of VDRA in March 2015, and 35 patients who discontinued VDRA between dialysis initiation and March 2015. Finally, 967 patients participated in the present study.

Patient characteristics and data at the time of dialysis initiation (baseline)

We defined the baseline as time of dialysis initiation. The patients' body mass index (BMI) was measured at the first dialysis session, and we checked their cardiovascular history categorized as coronary artery disease, valvular heart disease, and congestive heart failure requiring hospitalization, cerebral infarction, cerebral hemorrhage, or aortic disease from medical records. and We defined comorbidity of diabetes as fasting blood glucose level ≥ 126 mg/dL, random blood glucose level ≥ 200 mg/dL, HbA1c level (National Glycohemoglobin Standardization Program) $\geq 6.5\%$, use of insulin, or use of oral hypoglycemic agents. Before the first dialysis session, blood samples were taken for laboratory testing, and the patients'

blood pressure was measured. Aortic calcification was assessed according to the presence or absence of aortic arch calcification on plain frontal chest radiographs taken immediately before dialysis initiation. Cardiac valve calcification was assessed according to the presence or absence of a calcified aortic or mitral valve determined by B-mode echocardiography during the 1-month periods before and after dialysis initiation. Information about drug usage was also obtained from the patients' medical records. Use of VDRA and angiotensin converting enzyme inhibitor (ACEI) / angiotensin receptor blocker (ARB) were considered as medication at the time of dialysis initiation if they had been used at least 3 months before. However, other medication use refers to the drugs taken by the patients at the time of dialysis initiation.

Classification according to usage of VDRA

Prescriptions for VDRA were surveyed in March 2015 by medical records or questionnaires to other institutions. We classified the participating patients into three groups according to use of VDRA in March 2015: No use of VDRA (NV group), oral VDRA (OV group), and intravenous VDRA (IV group).

Outcomes

Survival prognosis as of September 30, 2016, was determined from the patients' medical records. For patients who were transferred to other institutions, information was obtained using a mail survey. The starting point of survival time was set in March 2015. We defined five outcomes and compared them among the three groups: 1) all-cause mortality, 2) cardiovascular (CV)-related mortality, 3) infection-related mortality, 4) cancer-related mortality, and 5) non-cancer-related mortality. Cardiovascular death was defined as death caused by heart failure, acute coronary syndrome, stroke, or cardiogenic sudden death.

Subgroup analysis

The main three groups were divided into five groups according to usage of VDRA at dialysis initiation and in March 2015 as: No use of VDRA at both points (Subgroup 1), use of oral VDRA in March 2015 but not at dialysis initiation (Subgroup 2), use of oral VDRA at both points (Subgroup 3), use of intravenous VDRA in March 2015 but not at dialysis initiation (Subgroup 4), and use of oral VDRA at dialysis initiation and intravenous VDRA in March 2015 (Subgroup 5). We compared all-cause mortality among the five groups.

Statistical analysis

SPSS version 24 (IBM Corporation, New York, US) and the Easy R program (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [18] were used for statistical analysis. For continuous variables, patient characteristics and baseline data were compared between the three groups using analysis of variance. Fisher's exact test was used for nominal variables. Mortality rates were compared among the three groups using the log-rank test on Kaplan–Meier curves. Factors contributing to the all-cause mortality rates were examined using univariate Cox proportional hazard regression analysis. In addition

to the three groups, factors that were significant in the univariate analysis served as explanatory variables for the multivariate Cox proportional hazard analysis using the stepwise method (i.e. comorbidity of diabetes, history of cardiovascular disease, BMI, diastolic blood pressure, aortic calcification, estimated glomerular filtration rate [eGFR], serum phosphate, serum magnesium, and use of ACEI / ARB). In addition, to test all-cause mortality among the five groups, we conducted Cox proportional hazard analysis by setting models. In stratified analyses, all-cause mortality rates were compared by univariate Cox proportional hazard models. Model 1: Adjusted for age and gender; Model 2: Adjusted for Model 1 plus comorbidity of diabetes, history of cardiovascular disease, BMI, diastolic blood pressure, aortic calcification, eGFR, serum phosphate, serum magnesium, and use of ACEI/ARB; and Model 3: Adjusted for Model 2 plus serum-adjusted calcium. Continuous variables are expressed as mean $\pm$ standard deviation, or as median (interquartile range); categorical variables are presented as a percentage. All p-values less than 0.05 were considered statistically significant.

Results

Comparison of patient characteristics and baseline data among the three groups

Table 1 shows patient characteristics and baseline data. The mean follow-up period was 506 days and there were no significant differences ($p = 0.439$) between the three groups (NV, OV and IV groups). The following parameters differed among the three groups: gender, comorbidity of diabetes, serum alkaline phosphatase, serum-adjusted calcium, serum-intact PTH, serum calcitriol, bicarbonate, and use of phosphate binders.

Comparison of all-cause mortality

Figure 2 shows Kaplan-Meier curves for the cumulative survival rates of the three groups. There were 104 deaths during the follow-up period (NV group, 27 cases; OV group, 53 cases; IV group, 24 cases). Significant differences between the cumulative survival rates were observed for the three groups ($p = 0.010$).

Comparison of types of mortality

Figure 3 displays the Kaplan–Meier curves for the three groups in terms of CV-related mortality (Figure 3A), infection-related mortality (Figure 3B), cancer-related mortality (Figure 3C), and non-cancer-related mortality (Figure 3D). Significant differences between non-cancer-related mortality were observed for the three groups ($p = 0.027$). However, no significant differences between the CV-related, infection-related, and cancer-related mortality were observed for the three groups ($p = 0.243$, $p = 0.228$, and $p = 0.393$, respectively).

Hazard ratios for all-cause mortality among the three groups

In the univariate regression analyses (Table 2), all-cause mortality rates were significantly lower for the IV group than for the NV group (hazard ratio [HR] = 0.44, 95% confidence interval [CI] = 0.25–0.76, $p =$

0.003), but not significantly different for the OV group (HR = 0.75, 95%CI = 0.47–1.19, $p = 0.225$). In addition, all-cause mortality was associated with some factors including age, gender, history of cardiovascular disease (CVD), BMI, diastolic blood pressure, aortic calcification, eGFR, serum-adjusted calcium, serum phosphate, serum magnesium, and use of ACEIs / ARBs. The results of multivariate Cox proportional hazard analysis using the stepwise method are shown in Table 3. The IV group was associated with low all-cause mortality as compared with the NV group (HR = 0.46, 95% CI = 0.24–0.89, $p = 0.02$). In addition, high mortality was associated with advanced age, male gender, and increase in serum-adjusted calcium.

Comparison of all-cause mortality and hazard ratios among the five subgroups

Significant differences between the cumulative survival rates were observed for the five subgroups ($p = 0.042$) (Supplementary Figure). Figure 4 shows hazard ratio (HR) for all-cause mortality among the five subgroups. All-cause mortality rates were significantly lower for subgroup 4 than subgroup 1 in model 1 (HR = 0.30, 95% CI; 0.11–0.86, $p = 0.02$). Furthermore, all-cause mortality rates were significantly lower for subgroup 5 than subgroup 1 in models 1 and 2 (HR = 0.43, 95% CI = 0.24–0.77, $p = 0.004$; HR = 0.47, 95% CI = 0.23–0.96, $p = 0.038$, respectively). However, no significant differences for mortality were observed between subgroups 1 and 5 in model 3 (HR = 0.53, 95% CI = 0.26–1.09, $p = 0.083$).

Discussion

The present study demonstrated that early introduction of IV VDRA to incident dialysis patients was associated with better prognosis. The features of this study were: 1) We could observe the effects of VDRA for mortality in the early period after dialysis initiation, 2) we could consecutively observe the clinical course from dialysis initiation to maintenance dialysis, and 3) we could conduct the study, based in real world clinical settings.

Previous studies have shown that VDRA can provide several benefits for CKD patients besides classical actions including calcium metabolism. In CKD patients, both oral and intravenous VDRA or native vitamin D were suggested to improve their prognosis [19, 20]. The mechanisms for that are still under discussion, however the pleiotropic effects of the regulating renin-angiotensin system and reducing infectious diseases have been reported thus far [6, 21, 22]. Some papers also reported that VDRA may prevent left-ventricular hypertrophy. Meanwhile, the randomized control PRIMO [23] and OPERA [24] studies, did not demonstrate that paricalcitol improves left ventricular hypertrophy in pre-dialysis patients. Therefore, this remains controversial [8, 23–25]. Obi et al have reported that the early use of VDRA within at least 2 years after dialysis initiation, was associated with lower infection-related mortality in the Japanese nationwide registry data [26]. Although when VDRA should be introduced to CKD patients remains controversial, VDRA was used within at least 3.5 years after dialysis initiation in our study, similarly to the Japanese nationwide data. According to the decline of kidney function, the serum calcitriol level decreases to below the normal lower limit far earlier before dialysis initiation. Hence, our results suggested initiation of VDRA use should be considered before decline of residual kidney function. There were some problems in

previous reports dealing with the association between VDRA or native vitamin D and survival. Most studies were conducted in an observational manner. Meanwhile, recently, Shoji et al showed that oral VDRA use for hemodialysis patients without secondary hyperparathyroidism could not improve survival rate in a large-scale randomized control trial in Japan [27]. In the study, over 900 patients were enrolled and mortality and CVD events were compared between the two groups with or without oral VDRA use. Compared to our study, the period on dialysis of the patients enrolled in the study was longer. We could not directly indicate that VDRA use improves survival because of the observational method. We also indicated that the patients, who had taken oral VDRA before initiation of dialysis and continued it, showed relatively better prognosis than who had not. Therefore, we considered that the earlier the initiation of VDRA, the greater the benefits for CKD patients.

Moreover, researchers are unsure which to choose, intravenous or oral VDRA and when to start or discontinue VDRA or native vitamin D supplementation for survival in CKD patients. Native vitamin D is activated by CYP2R1 and CYP27B1, in the liver and kidneys, respectively [28]. Interestingly, 25-dihydroxyvitamin D can change to calcitriol in different types of cells including monocytes and parathyroid cells [16]. Moreover, calcitriol could act in a paracrine and autocrine manner. Some studies showed that the calcitriol produced locally could also play an important role in pleiotropic vitamin D actions [29, 30]. Unfortunately, native vitamin D was not available in Japan because insurance did not support the use of it. Therefore, we usually use VDRA in real world clinical settings and also in the present study.

Basically, this study compared the prognosis of the three groups divided according to route of administration of VDRA and it revealed that IV VDRA could lead to better prognosis with regard to all-cause mortality. However, this favorable effect of intravenous VDRA remains unclear. Considering the fact that patients chosen to intravenous group presented lower serum calcium and higher serum intact-PTH, as one of the hypotheses, the subject of our investigation was in relatively early in the course of dialysis and had not had irreversible hyperparathyroidism yet. This may be why they reacted well to high concentration of VDRA by intravenous way and their hyperthyroidism was suppressed. Although we did not collect trends of serum calcium levels except for baseline, they could have affected the prognosis because multivariate analysis for all-cause mortality was no longer significant if serum-adjusted calcium at the baseline was added to the subgroup analysis model. Previous reports showed that intravenous maxacalcitol did not comparably increase serum calcium levels [31, 32]. The reason significant effects were not observed in terms of CV- and infectious-related deaths may be due to insufficiency of power, in fact, there were merely about 10 deaths in each group.

The limitations of this study are: First, this is an observational study, and there could remain indeterminate factors regardless of using multivariate analysis. Second, because of lack of information, we could not exclude the patients who had passed away by the surveillance in March 2015. Hence, we could not clarify the relationship between VDRA use and mortality in patients with shorter survival periods after dialysis initiation. We could collect laboratory data only at baseline. Third, the criteria for initiation of dialysis and rules for use of VDRA and calcimimetics were undetermined. However, all physicians of

participating facilities who decided to start dialysis were certified as nephrologists by the Japanese Society of Nephrology. Therefore, we assumed that there were few differences in the timing of dialysis initiation among patients.

Conclusions

In conclusion, early introduction of intravenous VDRA for patients on hemodialysis was suggested to be associated with better prognosis. Strict management of calcium and phosphate is a prerequisite. Prospective randomized control studies are needed in the future.

Abbreviations

ACEI: Angiotensin converting enzyme inhibitor

AICOPP: Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis

ARB: angiotensin receptor blocker

BMI: Body mass index

CI: confidence interval

CKD: Chronic kidney disease

CKD-MBD: Chronic kidney disease-mineral and bone disorder

CV: cardiovascular

CVD: cardiovascular disease

eGFR: estimated glomerular filtration rate

HR: hazard ratio

KDIGO: Kidney Disease Improving Global Outcomes

PTH: Parathyroid hormone

VDRA: Vitamin D receptor activator

Declarations

Ethics approval and consent to participate

This study was conducted according to the Ethical Guidelines for Clinical Research by the Japanese Ministry of Health, Labor, and Welfare (created on July 30, 2003; full revision on December 28, 2004; full revision on July 31, 2008) and the Helsinki Declaration (revised in 2013), and was approved by the clinical research ethics committees at each AICOPP group facility (approval number: 20110823–3). The subjects received oral and written explanations of the purpose of the study and provided written consent. The trial registration no. is UMIN 000007096, registered on January 18, 2012.

Consent for publication

This results have not been published previously in whole or part, except in abstract form (55th ERA-EDTA Congress, Copenhagen, Denmark, 2018).

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

YY has received research support grants from Otsuka Pharmaceutical Co., Ltd, Kyowa Hakko Kirin Co., Ltd, and Chugai Pharmaceutical Co., Ltd. DI has received lecture fees from Ono Pharmaceutical Co., Ltd, Kyowa Hakko Kirin Co., Ltd. Other authors have nothing to declare.

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Authors' contributions

DI participated in the design of the study and interpretation of data. EKI, DI, and SK participated in writing the manuscript. KT, HH, NT, MH, and YY participated in analysis of data. All authors were involved in drafting, reviewing, and have approved the final manuscript for submission.

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Tables

Table 1. Baseline characteristics and laboratory data

Variables	No VDRAs	Oral VDRAs	IV VDRAs	p value
	n, 177	n, 447	n, 343	
Age (years old)	67.2, 12.7	66.5, 12.2	67.3, 13.1	0.678
Female Gender (%)	42.9	31.1	35.9	0.018
Diabetes Mellitus (%)	63.3	58.8	48.1	0.001
History of CAD (%)	13.0	15.2	13.5	0.680
History of Stroke (%)	15.8	16.1	12.5	0.342
History of CVD (%)	42.4	43.8	37.9	0.234
BMI (kg/m ²)	23.9, 4.9	23.7, 4.2	24.2, 4.8	0.217
SBP (mmHg)	155, 29	154, 25	152, 26	0.446
DBP (mmHg)	77, 16	78, 15	78, 15	0.746
Aortic Calc (%)	37.5	33.8	36.3	0.618
Aortic Valve Calc (%)	31.8	28.2	30.3	0.672
Follow up period (day)	491, 179	508, 160	512, 162	0.439
Laboratory data				
Hemoglobin (g/dL)	9.3, 1.5	9.5, 1.5	9.3, 1.6	0.075
Albumin (g/dL)	3.14, 0.58	3.19, 0.61	3.25, 0.60	0.116
ALP (IU/L)	231, 87	248, 129	278, 134	< 0.001
Uric Acid (mg/dL)	9.1, 2.6	8.6, 2.3	8.7, 2.6	0.103
BUN (mg/dL)	92.1, 30.0	90.4, 27.1	91.9, 34.2	0.724
Creatinine (mg/dL)	8.84, 3.26	9.10, 2.99	9.39, 3.66	0.172
eGFR (ml/min/1.73m ²)	5.3, 2.0	5.4, 2.4	5.1, 1.7	0.096
Adjusted Calcium (mg/dL)	8.8, 1.1	8.6, 1.0	8.4, 1.0	< 0.001
Phosphate (mg/dL)	6.5, 1.8	6.3, 1.8	6.4, 2.0	0.409
Magnesium (mg/dL)	2.3, 0.6	2.2, 0.5	2.1, 0.5	0.001
LDL-C (mg/dL)	94, 40	89, 31	89, 35	0.266
HDL-C (mg/dL)	46, 18	45, 17	44, 16	0.478
TG (mg/dL)	125, 58	127, 64	124, 86	0.882
Ferritin* (ng/mL)	131 [76, 272]	122 [63, 207]	121 [59, 203]	0.786
Intact PTH* (pg/mL)	244 [158, 335]	260 [186, 381]	407 [281, 591]	< 0.001
1,25(OH) ₂ vitamin D (pg/mL)	10.6, 4.6	14.3, 8.1	14.3, 8.1	0.004
Bicarbonate (mmol/L)	20.0, 5.2	19.7, 4.6	18.8, 4.7	0.016
CRP* (mg/dL)	0.31 [0.10, 1.43]	0.26 [0.10, 1.14]	0.24 [0.11, 1.09]	0.169
Medication				
ACEIs / ARBs (%)	67.8	61.0	60.3	0.211
CCBs (%)	74.6	81.2	83.4	0.052
Loop diuretics (%)	67.2	66.9	65.3	0.866
bBs (%)	31.6	33.8	33.5	0.872
Statins (%)	36.7	40.5	41.1	0.603
VDRAs (%)	0.0	33.1	25.1	< 0.001
Phosphate binders (%)	33.9	42.1	34.1	0.037
NaHCO ₃ (%)	42.9	46.5	46.9	0.657
ESAs (%)	85.3	87.2	88.9	0.496

Mean, standard deviation, * Median [1st quartile, 3rd quartile]

VDRA; vitamin D receptor activator, IV; intravenous, CAD; coronary artery disease, CVD; cardiovascular disease, BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, Calc; calcification, ALP; alkaline phosphatase, BUN; blood urea nitrogen, eGFR; estimated glomerular filtration rate, LDL-C; low density lipoprotein cholesterol, HDL-C;

high density lipoprotein cholesterol, TG; triglyceride, PTH; parathyroid hormone, CRP; C reactive protein, ACEI; angiotensin converting enzyme, ARB; angiotensin receptor blocker, CCB, calcium channel blocker, bB; b blocker, VDRA; vitamin D receptor activator, ESA; erythropoiesis stimulating agent

Table 2. Associations of variables with all-cause mortality according to the univariate Cox proportional hazard regression analysis

Variables	Hazard Ratio	95% CI	p value
IV VDRAs vs No VDRAs	0.44	0.25-0.76	0.003
Oral VDRAs vs No VDRAs	0.75	0.47-1.19	0.225
Age (10 years old)	2.06	1.68-2.53	< 0.001
Female Gender	0.54	0.34-0.85	0.005
Diabetes Mellitus	1.12	0.76-1.66	0.560
History of CAD	1.46	0.90-2.38	0.129
History of Stroke	1.59	0.99-2.54	0.054
History of CVD	2.07	1.40-3.05	< 0.001
BMI (1 kg/m ²)	0.93	0.88-0.98	0.005
SBP (10 mmHg)	0.99	0.93-1.06	0.801
DBP (10 mmHg)	0.90	0.91-1.00	0.050
Aortic Calc	1.87	1.28-2.75	0.001
Aortic Valve Calc	1.39	0.90-2.16	0.143
Hemoglobin (1 g/dL)	1.10	0.97-1.26	0.131
Albumin (1 g/dL)	0.82	0.60-1.12	0.215
ALP (10 IU/L)	1.01	0.99-1.02	0.289
Uric Acid (mg/dL)	1.00	0.93-1.09	0.945
BUN (10 mg/dL)	1.02	0.96-1.09	0.476
Creatinine (1 mg/dL)	0.86	0.80-0.93	< 0.001
eGFR (1 ml/min/1.73m ²)	1.09	1.02-1.16	0.010
Adjusted Calcium (1 mg/dL)	1.38	1.14-1.67	0.001
Phosphate (1 mg/dL)	0.83	0.74-0.94	0.003
Magnesium (1 mg/dL)	1.53	1.07-2.19	0.020
LDL-C (10 mg/dL)	0.96	0.90-1.03	0.220
HDL-C (10 mg/dL)	1.11	0.98-1.24	0.101
TG (10 mg/dL)	1.01	0.98-1.03	0.538
Ferritin* (1 ng/mL)	1.00	0.99-1.00	0.917
Intact PTH* (1 pg/mL)	1.00	0.99-1.00	0.180
Bicarbonate (1 mmol/L)	1.03	0.99-1.08	0.193
CRP* (1 mg/dL)	1.03	0.98-1.07	0.229
ACEIs / ARBs	0.64	0.44-0.94	0.023
CCBs	1.09	0.65-1.80	0.754
Loop diuretics	1.15	0.76-1.75	0.503
bBs	1.00	0.66-1.50	0.989
Statins	0.72	0.47-1.08	0.108
Phosphate binders	0.70	0.46-1.07	0.096
NaHCO ₃	0.97	0.66-1.43	0.882
ESAs	0.96	0.54-1.72	0.901

CI; confidence interval, IV; intravenous, VDRA; vitamin D receptor activator, CAD; coronary artery disease, CVD; cardiovascular disease, BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, Calc; calcification, ALP; alkaline phosphatase, BUN; blood urea nitrogen, eGFR; estimated glomerular filtration rate, LDL-C; low density lipoprotein cholesterol, HDL-C; high density lipoprotein cholesterol, TG; triglyceride, PTH; parathyroid hormone, CRP; C reactive protein, ACEI; angiotensin converting enzyme, ARB; angiotensin receptor blocker, CCB, calcium channel blocker, bB; b blocker, ESA; erythropoiesis stimulating agent

Table 3. Associations of variables with all-cause mortality according to the multivariate Cox proportional hazard regression analysis

Variables	Hazard Ratio	95%CI	p value
IV VDRA vs No VDRA	0.46	0.24-0.89	0.022
Age (10 years old)	2.04	1.56-2.67	< 0.001
Female Gender	0.42	0.23-0.77	0.005
Adjusted Calcium (1 mg/dL)	1.49	1.13-1.96	0.005

CI; confidence interval, IV; intravenous, VDRA; vitamin D receptor activator

Adjusted for DM, history of CVD, BMI, DBP, aortic calcification, eGFR, serum phosphate, serum magnesium, and use of ACEIs / ARBs

DM; diabetes mellitus, CVD; cardiovascular disease, BMI; body mass index, DBP; diastolic blood pressure, eGFR; estimated glomerular filtration rate, ACEI, angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker

Figures

Figure 1

Figure 1

Participated patients flow.

Figure 2

Figure 2

Kaplan-Meier curves for the cumulative survival between the three groups. Significant differences between the cumulative survival rates were observed for the three groups ($P = 0.010$). IV; intravenous VDRA group, OV; oral VDRA group, NV; no VDRA group

Figure 3

Figure 3

Kaplan-Meier curves for the cumulative survival for each cause of death between the three groups. A: Comparison of cardiovascular related mortality, B: Comparison of infection related mortality, C: Comparison of cancer related mortality, D: Comparison of non-cancer related mortality. Significant differences between the non-cancer-related mortality were observed for the three groups ($P = 0.027$). IV; intravenous VDRA group, OV; oral VDRA group, NV; no VDRA group

Figure 4

Figure 4

Hazard ratio for all-cause mortality among the five subgroups. All-cause mortality rates were significantly lower for the Subgroup 4 than the Subgroup 1 in model 1 (HR = 0.30, 95% CI = 0.11–0.86, P = 0.024). All-cause mortality rates were significantly lower for the Subgroup 5 than the Subgroup 1 in model 1 and 2 (HR = 0.43, 95% CI = 0.24–0.77, P = 0.004, HR = 0.47, 95% CI = 0.23–0.96, P = 0.038, respectively). a: no use of VDRA at the both of two points (Subgroup 1) b: use of oral VDRA in March 2015 not at dialysis initiation (Subgroup 2) c: use of oral VDRA at the both of two points (Subgroup 3), d: use of intravenous VDRA in March 2015 not at dialysis initiation (Subgroup 4) e: use of oral VDRA at dialysis initiation and intravenous VDRA in March 2015 (Subgroup 5) Model 1: adjusted for age and gender Model 2: adjusted for Model 1 plus comorbidity of diabetes, history of cardiovascular disease, BMI, diastolic blood pressure, aortic calcification, eGFR, serum phosphate, serum magnesium, and use of ACEI / ARB Model 3: adjusted for Model 2 plus serum adjusted calcium.

Supplementary Files

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