Lanthanum Carbonate and Survival in Maintenance Haemodialysis Patients -Tokai Dialysis Cohort Study-

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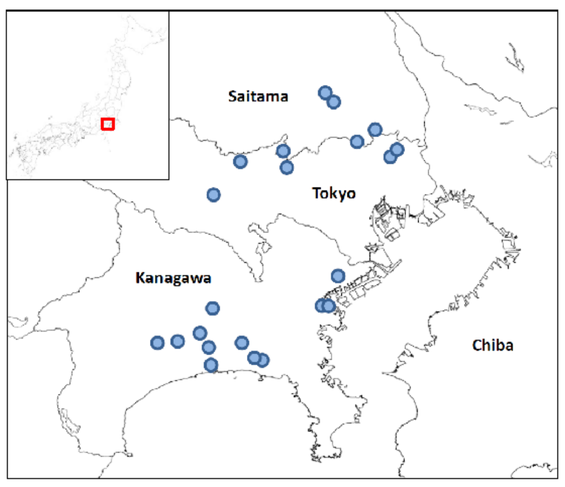
Introduction and Aims

- Hyperphosphataemia is a risk factor for mortality on dialysis, and phosphate binders are used in the majority of dialysis patients.
- Lanthanum carbonate (LC) is a non-calcium phosphate binder that is effective for the treatment of hyperphosphataemia in dialysis patients.
- We have previously shown that LC is effective even in patients with uncontrolled hyperphosphataemia with conventional therapy (Goto S et al. Clin J Am Soc Nephrol 6, 2011).
- A recent pilot trial has shown reduced progression of aortic calcification with LC compared with calcium carbonate (Toussaint ND, et al. Nephrology 16, 2011).
- However, there are limited data on whether treatment with LC affects survival.

Methods

- Data were from Tokai Dialysis Cohort Study, a retrospective cohort study of 2,292 patients receiving maintenance haemodialysis as of 31 December 2008 (immediately prior to the commercial availability of LC in Japan).
- Patients who died within the first 3 months of follow-up and those with missing data on LC prescription were excluded from the analysis (n = 23).
- We compared all-cause mortality among patients who began treatment with LC (LC group; n = 666) with those who remained untreated (control group; n = 1,603).
- For the LC group, follow-up time started within 1 month prior to first LC prescription. For the control group, follow-up time started on 31 December 2008 in all cases.
- In an effort to mimic a randomized trial, we performed an intention-to-treat analysis in which patients who started to receive LC were analyzed in the LC group regardless of subsequent "crossover" to control.
- We also compared survival in a subcohort of LC-treated (n = 564) and untreated (n = 564) patients matched by the propensity score of receiving LC.



Results

Table 1. Baseline characteristics of LC and control in the overall unmatched cohort and the propensity score-matched cohort

	Unmatched Cohort			Propensity Score-Matched Cohort		
	Control (n = 1,603)	LC (n = 666)	P	Control (n = 564)	LC (n = 564)	P
Age (yr)	67±12	60±12	<0.001	61±13	61±12	0.65
Male (%)	63.1	65.5	0.28	64.5	64.5	1.0
Duration of dialysis (mo)	62(29-127)	76(32-152)	<0.001			0.28
Genesis of renal failure (%)						
Glomerulonephritis	23.3	27.0	0.005	28.4	28.2	0.75
Diabetes	37.2	30.9		30.0	30.3	
Pyelonephritis	1.6	1.2		2.3	1.1	
Polycystic kidney disease	3.1	3.0		3.4	3.4	
Hypertension	8.7	6.5		6.9	6.6	
Others	15.0	20.1		18.6	18.3	
Unknown	11.2	11.3		10.5	12.2	
Systolic blood pressure (mmHg)	150±24	150±23	0.97	150±24	150±23	0.96
Diastolic blood pressure (mmHg)	77±14	80±14	<0.001	79±14	80±14	0.53
BMI (kg/m^2)	21.2±3.4	21.6±3.4	0.01	21.3±3.5	21.6±3.3	0.16
Vascular access (%)						
Fistula	90.7	94.4	0.005	93.3	93.6	0.76
Graft	6.1	4.2		4.6	4.8	
Subcutaneously-fixed superficial artery	2.3	1.1		1.8	1.2	
Catheter	0.8	0.0		0.2	0.0	
Others	0.1	0.3		0.2	0.4	
Coronary artery disease (%)	17.6	16.8	0.66	17.4	15.4	0.38
Stroke (%)	15.0	9.3	<0.001	9.2	10.5	0.48
Peripheral artery disease (%)	8.5	8.9	0.77	9.6	8.5	0.53
History of fracture (%)	8.7	8.0	0.55	7.8	7.3	0.74
History of parathyroidectomy (%)	4.7	8.6	<0.001	8.9	8.0	0.59
Kt/V	1.29±0.25	1.27±0.25	0.06	1.29±0.25	1.28±0.25	0.50
nPCR	0.85±0.16	0.92±0.16	<0.001	0.92±0.15	0.91±0.16	0.56
Haemoglobin (g/dl)	10.4±1.0	10.5±1.2	0.04	10.5±1.0	10.4±1.2	0.90
Albumin (g/dl)	3.7±0.3	3.8±0.3	<0.001	3.8±0.3	3.8±0.3	0.52
Creatinine (mg/dl)	11.2±3.0	12.8±2.8	<0.001	12.6±2.9	12.5±2.7	0.47
Corrected calcium (mg/dl)	9.0±0.8	9.3±0.8	<0.001	9.3±0.8	9.3±0.8	0.51
Phosphate (%)	5.2±1.3	6.3±1.3	<0.001	6.1±1.2	6.1±1.2	0.59
Intact PTH (%)	127(68-207)	152(68-255)	<0.001			0.94
Alkaline phosphatase (U/l)	283(185-306)	216(170-275)	<0.001			0.57
Total cholesterol (mg/dl)	159±34	159±34	0.88	160±35	160±34	0.99
Use of calcium carbonate (%)	79.1	80.9	0.32	81.2	82.1	0.70
Use of sevelamer hydrochloride (%)	23.5	43.7	<0.001	39.4	40.2	0.76
Use of VDRA (%)	56.7	59.9	0.09	60.6	60.1	0.86

Table 2. Cox proportional hazards analysis of mortality comparing LC with control in the overall unmatched cohort, stratified by baseline serum phosphate

Model	All patients		Serum phosphate ≤6.0 mg/dl		Serum phosphate >6.0 mg/dl	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
1	0.46 (0.32-0.66)	<0.001	0.56 (0.33-0.93)	0.024	0.39 (0.23-0.67)	0.001
2	0.84 (0.58-1.23)	0.38	1.21 (0.71-2.05)	0.49	0.51 (0.29-0.90)	0.019
3	0.72 (0.48-1.08)	0.11	1.17 (0.68-2.02)	0.57	0.54 (0.30-0.97)	0.039

Model 1: unadjusted
Model 2: age, sex, cause of renal failure, and dialysis vintage, mean blood pressure, BMI, vascular access, coexisting conditions, Kt/V, and nPCR
Model 3: Model 2 plus albumin, haemoglobin, creatinine, corrected calcium, phosphate, intact PTH, alkaline phosphatase, total cholesterol, use of calcium carbonate, use of sevelamer hydrochloride, and use of VDRA

Table 3. Effect of cut points for stratification by serum phosphate on Cox proportional hazards analysis of mortality with LC in the overall unmatched cohort

Cut point for stratification	HR	95% CI	P
No stratification	0.72	0.48-1.08	0.11
Serum phosphate >3.5 mg/dl	0.69	0.46-1.04	0.080
Serum phosphate >4.5 mg/dl	0.67	0.44-1.02	0.062
Serum phosphate >5.5 mg/dl	0.62	0.37-1.02	0.058
Serum phosphate >6.0 mg/dl	0.54	0.30-0.97	0.039
Serum phosphate >6.5 mg/dl	0.43	0.20-0.95	0.036

Model 3: age, sex, cause of renal failure, and dialysis vintage, mean blood pressure, BMI, vascular access, coexisting conditions, Kt/V, nPCR, albumin, haemoglobin, creatinine, serum calcium, serum phosphate, intact PTH, alkaline phosphatase, total cholesterol, use of calcium carbonate, use of sevelamer hydrochloride, and use of VDRA

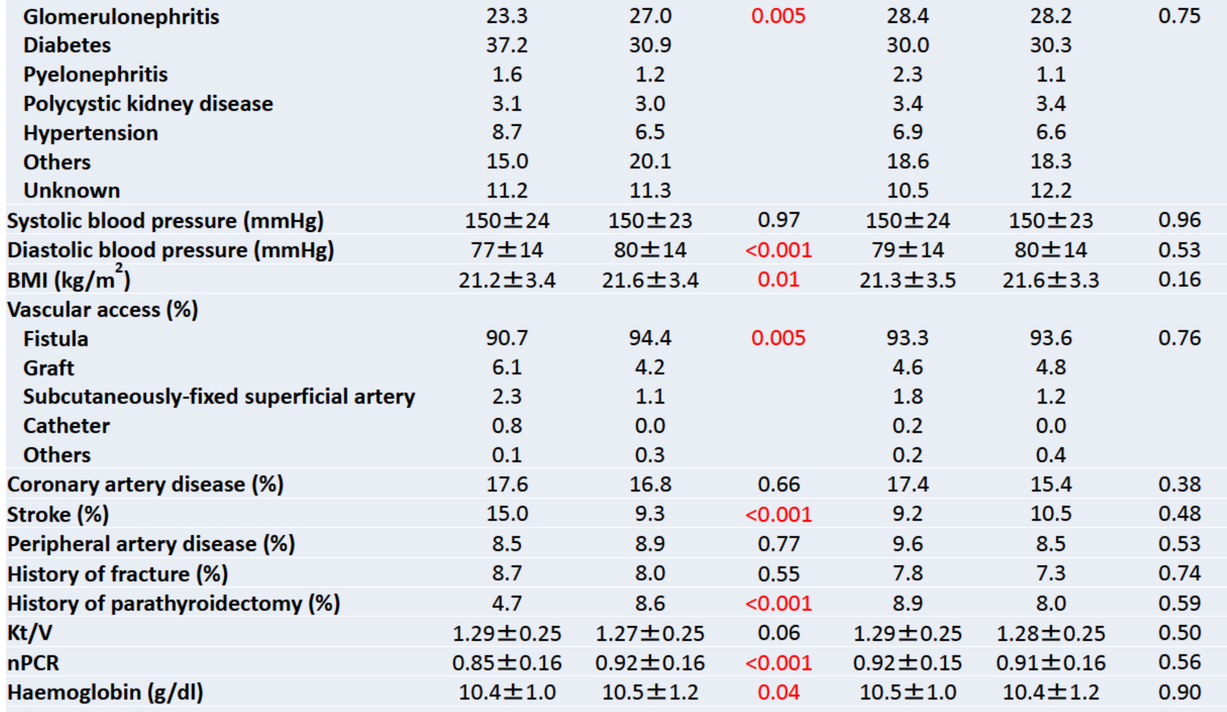


Figure 1. Percentage of patients treated with LC and mean daily dosage of LC during the study period

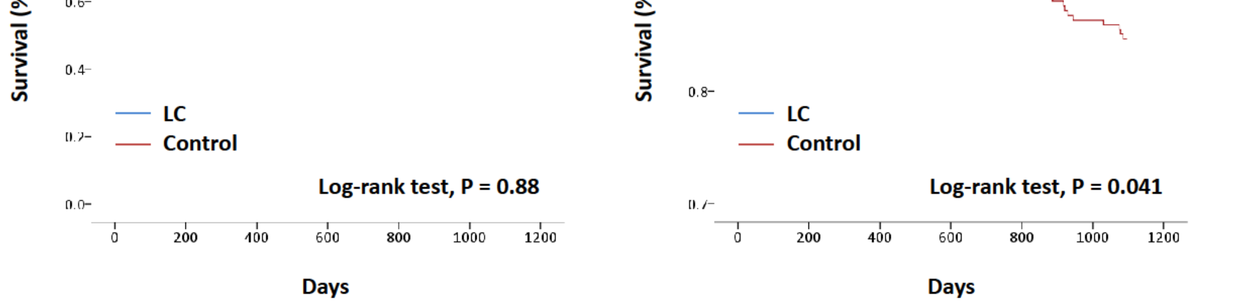


Figure 2. Kaplan-Meier analysis of survival comparing LC with control in the propensity-score matched cohort, stratified by baseline serum phosphate

Conclusions

- Treatment with LC was independently associated with survival benefit in maintenance haemodialysis patients with uncontrolled hyperphosphataemia.
- Randomized controlled trials are needed to determine whether LC actually improves survival among patients receiving maintenance haemodialysis.

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