Survival advantage of lanthanum carbonate for hemodialysis patients with uncontrolled hyperphosphatemia

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ABSTRACT

Background. Lanthanum carbonate is a non-calcium phosphate binder that is effective for the treatment of hyperphosphatemia. However, it is unknown whether treatment with lanthanum affects survival.

Methods. We retrospectively collected data on maintenance hemodialysis patients at 22 facilities (n = 2292) beginning in December 2008, a time point immediately prior to the commercial availability of lanthanum in Japan. We compared 3-year all-cause mortality among patients who initiated lanthanum (n = 560) and those who were not treated with lanthanum during the study period (n = 560) matched by the propensity score of receiving lanthanum. Several sensitivity analyses were performed to test the robustness of the primary analysis.

Results. After the market introduction of lanthanum, the percentage of patients receiving the binder increased gradually to 27%. In the propensity score-matched analysis, the mortality rate for the lanthanum group was not significantly lower than the non-lanthanum group [hazard ratio (HR), 0.71; 95% confidence interval (CI), 0.47–1.09]. However, stratification by serum phosphorus disclosed significant survival benefit of lanthanum for patients with serum phosphorus >6.0 mg/dL (HR, 0.52; 95% CI, 0.28–0.95), but not in patients with serum phosphorus ≤6.0 mg/dL (HR, 1.00; 95% CI, 0.55–1.84). The survival benefit of lanthanum in patients with serum phosphorus >6.0 mg/dL was consistent across subgroups and robust in different analytical approaches.

Conclusions. Treatment with lanthanum was independently associated with a significant survival benefit in hemodialysis patients with inadequately controlled hyperphosphatemia. Further studies are required to confirm these findings.

Keywords: hemodialysis, hyperphosphatemia, lanthanum carbonate, survival

INTRODUCTION

Hyperphosphatemia is one of most common complications of end-stage renal disease [1–3]. Elevated phosphorus has been shown to induce vascular calcification [4–6] and observational studies have consistently identified hyperphosphatemia as an independent risk factor for cardiovascular events and mortality [1–3]. Based on these data, several national and international clinical practice guidelines recommend control of serum phosphorus within specific ranges [7–9]. Because dietary restriction of phosphorus is not sufficient to control hyperphosphatemia and may exacerbate protein malnutrition, administration of oral phosphate binders is the cornerstone of therapy for hyperphosphatemia [10, 11]. However, despite the widespread use of phosphate binders such as calcium carbonate and sevelamer hydrochloride, >30% of dialysis patients worldwide still present with serum phosphorus levels >6 mg/dL [2], presumably because the adverse effects of these drugs, including hypercalcaemia and gastrointestinal symptoms, limit their use.

Lanthanum carbonate is a non-aluminum, calcium-free phosphate binder that became commercially available in the USA in 2005, in the EU in 2006 and in Japan in 2009. Clinical studies have shown that lanthanum is as effective as calcium-based binders in lowering serum phosphorus levels without causing hypercalcemia [12, 13] and that adding lanthanum improves control of serum phosphorus in patients who had inadequately controlled hyperphosphatemia with previous phosphorus-lowering therapy [14]. In addition, a small
randomized controlled trial demonstrated a slower progression of aortic calcification with lanthanum than with calcium-based binders [15]. However, it remains to be determined whether the use of lanthanum for treating hyperphosphatemia improves survival. We therefore conducted a historical cohort study of maintenance hemodialysis patients to test the hypothesis that addition of lanthanum is associated with improved survival.

MATERIALS AND METHODS

Study population
We performed a historical cohort study of 2292 maintenance hemodialysis patients at 22 dialysis facilities operated by the following medical corporations: Showakai, Boseikai, Seichikai, Seiwakai, Keyakikai, Yayoikai and Kuratakai. Patients were eligible for inclusion if they were at least 20 years of age and were receiving hemodialysis thrice weekly for >3 months as of 31 December 2008, immediately prior to the commercial availability of lanthanum in Japan (11 March 2009). Patients were followed until 31 December 2011, or until they were lost to follow-up. This study was approved by the Institutional Review Board of Tokai University School of Medicine, which waived the need for informed consent.

Data sources
Data on demographics, weight and height, hemodialysis prescription, vascular access, cardiovascular comorbidities (coronary artery disease, stroke and peripheral artery disease), history of fracture, history of parathyroidectomy and censoring (mortality, outside transfer and modality change) were collected retrospectively by medical record abstraction. Laboratory results and records of drug administration such as phosphate binders and vitamin D receptor activators (VDRAs) were collected prospectively and entered uniformly into a central database. These data were collected at baseline and at 3-month intervals from 31 December 2008 through 31 December 2011. Laboratory values included hemoglobin, albumin, creatinine, calcium, phosphorus, parathyroid hormone (PTH), alkaline phosphatase, total cholesterol, dialysis adequacy (Kt/V) and normalized protein catabolic rate (nPCR). Serum calcium levels were corrected for albumin concentration using Payne's formula [16]. Measurements of PTH were performed by the Elecsys intact PTH assay (F. Hoffmann-La Roche Ltd, Basel, Switzerland) at 21 facilities and by the Whole PTH assay (Scantibodies Laboratories, Santee, CA, USA) at one facility. Whole PTH levels were converted to intact PTH levels by the following equation: intact PTH = whole PTH × 1.7 [9].

Outcomes and exposures
The primary outcome was 3-year all-cause mortality. The primary exposure was initiation of lanthanum. We compared the survival of patients who started lanthanum with the survival of patients who were not treated with lanthanum during the study period. To adjust for covariates measured at the time the decision was made to initiate therapy, follow-up time for the lanthanum group started within 3 months prior to first lanthanum prescription, whereas follow-up time for the non-lanthanum group started on 31 December 2008. Because all patients in the lanthanum group survived at least 3 months of follow-up, we excluded those who were censored during the first 3 months in the non-lanthanum group from the analysis to match the conditions between the two groups. In an effort to mimic an intention-to-treat analysis, patients who initiated lanthanum conservatively stayed in the lanthanum group for all further analyses.

To minimize potential confounding and selection biases in this observational study, we compared the mortality rate between the lanthanum group and the non-lanthanum group using propensity score-matching analysis. The propensity for lanthanum prescription was determined by logistic regression analysis using the following variables: age, sex, duration of dialysis, primary cause of renal failure, mean blood pressure, body mass index (BMI), vascular access, coronary artery disease, stroke, peripheral artery disease, history of fracture, history of parathyroidectomy, Kt/V and nPCR, albumin, hemoglobin, creatinine, calcium, phosphorus, intact PTH, alkaline phosphatase, total cholesterol, use of calcium carbonate, use of sevelamer hydrochloride and use of VDRA. This model achieved a C statistic of 0.80, indicating reasonable discrimination between lanthanum users and nonusers. We created propensity score-matched pairs of patients who were treated with lanthanum and those who were not treated, with a caliper of 0.03.

Statistical analysis
We used the χ²-test, Student’s t-test and Wilcoxon rank-sum test to compare baseline characteristics and laboratory results between the lanthanum group and the non-lanthanum group. Changes in serum phosphorus during the study period were analyzed using repeated measures analysis of variance (ANOVA) followed by the Bonferroni post hoc test. We examined the risk of death associated with serum phosphorus levels in the full cohort using multivariate Cox regression, adjusted for age, sex, duration of dialysis, primary cause of renal failure, mean blood pressure, BMI, vascular access, coronary artery disease, stroke, peripheral artery disease, history of fracture, history of parathyroidectomy, Kt/V, nPCR, albumin, hemoglobin, creatinine, calcium, alkaline phosphatase, total cholesterol and use of VDRA. The proportional hazards assumption was tested using log-log plots.

We compared the mortality rate between the lanthanum group and the non-lanthanum group using propensity score-matching analysis. Because the matching strategy eliminated all differences in baseline characteristics between the two groups, we compared their survival using the Kaplan–Meier method and univariate Cox regression. Because lanthanum is used for treatment of hyperphosphatemia and elevated phosphorus is associated with a risk of death [1–3], the survival effect of lanthanum may be more pronounced in patients with uncontrolled hyperphosphatemia; therefore, we stratified patients according to whether they had uncontrolled hyperphosphatemia. Uncontrolled hyperphosphatemia was defined as serum phosphorus >6.0 mg/dL, according to the Japanese Society for Dialysis Therapy (JSDT) guideline [9]; this cutoff value was also a median of serum phosphorus levels in the propensity score-matched cohort. We performed several sensitivity analyses to test the robustness of our findings: [1] stratification by facility-specific standardized
mortality rate (SMR); [2] follow-up for the lanthanum group starting at the time of first lanthanum prescription and [3] time-dependent analysis that modelled lanthanum prescription as a time-dependent covariate. We also applied two other propensity score methods, namely, stratified Cox regression on quintiles of the estimated propensity score, and Cox regression adjusting for propensity score as a covariate. Conventional multivariable Cox regression, without using propensity score, was also performed.

For survival analysis, we replaced missing data using multiple imputation with five imputed datasets. Statistical analyses were performed on each imputed dataset and finally were pooled to achieve single parameter estimates. P < 0.05 was considered statistically significant. All of the analyses were performed using IBM SPSS Statistics 20 (IBM SPSS, Tokyo, Japan).

RESULTS

Patient characteristics

Of the 2292 patients in the entire cohort, we excluded 10 patients (0.4%) who died, 11 patients (0.5%) who transferred to other facilities (including hospitals) during the first 3 months of follow-up and 2 patients (0.1%) with missing data on lanthanum prescription. After exclusion, 2269 patients were available for analysis. Overall, the mean age was 64.9 years, 63.8% were male, 53.9% received dialysis for at least 5 years and 35.3% had diabetes as the cause of renal failure. These demographic characteristics were similar to those reported in a nationwide registry of Japanese dialysis patients as of 31 December 2008 [17].

After the market introduction of lanthanum in March 2009, the percentage of patients receiving the binder increased gradually to reach 27% by June 2011 (Figure 1). Baseline characteristics comparing patients who subsequently received lanthanum versus those who did not are summarized in Table 1. In the unmatched cohort, patients who initiated lanthanum were younger with longer dialysis duration; were less likely to have diabetes as a cause of renal failure; had a lower prevalence of stroke; were more likely to have history of parathyroidectomy; had a higher BMI, serum creatinine, calcium, phosphorus and PTH levels and were more likely to have a fistula for vascular access and receive sevelamer hydrochloride and intravenous VDRAs. In the propensity score-matched cohort, there were no differences in baseline characteristics between patients who received lanthanum and those who did not.

The initial daily mean ± SD dose of lanthanum was 821 ± 358 mg/day and increased gradually to reach a plateau of ~1000 ± 500 mg/day. More than 80% of these patients remained on lanthanum treatment over 2 years of observation (Table 2). Treatment with lanthanum was associated with significant reductions in the percentage of patients receiving other phosphate binders. In particular, the percentage of patients receiving calcium carbonate decreased approximately by half immediately after starting lanthanum. The percentage of patients receiving VDRAs remained unchanged in both groups. The mean serum phosphorus levels decreased significantly by 0.5 mg/dL and remained stable thereafter in patients who started lanthanum, while values remained unchanged in those who did not (Table 3).

Survival analysis

During a mean ± SD follow-up of 2.7 ± 0.7 years, 317 patients died (51.6/1000 person-years) in the entire cohort. After multivariable adjustment, serum phosphorus levels >6.4 mg/dL (highest quartile) were associated with an increased risk of death as compared with levels of 4.6–5.3 mg/dL [hazard ratio (HR), 1.49; 95% confidence interval (CI), 1.02–2.17; P = 0.04], a finding consistent with previous reports.

In the propensity score-matched cohort, the mortality rate for the lanthanum group was not significantly lower than the non-lanthanum group (31.3 versus 48.3 deaths/1000 patient-years; HR, 0.71; 95% CI, 0.47–1.09; P = 0.1) (Figure 2A). However, stratification by serum phosphorus disclosed significant survival benefit of lanthanum for patients with serum phosphorus >6.0 mg/dL (HR, 0.52; 95% CI, 0.28–0.95; P = 0.03) (Figure 2B), but not in patients with serum phosphorus ≤6.0 mg/dL (HR, 1.00; 95% CI, 0.55–1.84; P = 0.9) (Figure 2C). In both subgroups stratified by serum phosphorus, there were no differences in baseline characteristics between the two groups (data not shown). The survival advantage of lanthanum in patients with hyperphosphatemia was attenuated when the analysis included those with better controlled hyperphosphataemia (Table 4). Stratified analyses among patients with serum phosphorus >6.0 mg/dL showed a significant survival benefit of lanthanum in patients with longer dialysis duration, those with higher serum calcium and those not treated with calcium carbonate, whereas in no stratum was lack of treatment favored (Figure 3).

The survival advantage of lanthanum in patients with serum phosphorus >6.0 mg/dL was qualitatively unchanged when the analysis was stratified by facility-specific SMR (HR, 0.52; 95% CI, 0.27–0.97; P = 0.04), when we defined start of follow-up for the lanthanum group at the time of first lanthanum prescription (HR, 0.46; 95% CI, 0.25–0.83; P = 0.01), or when lanthanum was treated as a time-dependent covariate (HR, 0.46; 95% CI, 0.24–0.91; P = 0.02). Other propensity score-based approaches, stratification by propensity score and adjustment for propensity score as a covariate and conventional multivariable Cox regression without using propensity score yielded similar effects of lanthanum on survival in patients with uncontrolled hyperphosphatemia (Table 5).
no significant survival benefit of lanthanum was observed in patients with serum phosphorus ≤6.0 mg/dL in all of these sensitivity analyses (data not shown).

**DISCUSSION**

In this historical cohort study of maintenance hemodialysis patients, lanthanum prescription was associated with a significant survival advantage for patients who had inadequately controlled hyperphosphatemia, but not for those with controlled hyperphosphatemia. The benefit of lanthanum for patients with uncontrolled hyperphosphatemia was independent of established risk factors and robust to different analytic strategies, including propensity score methods. These data suggest a potential benefit of lanthanum to improve survival, particularly for patients with uncontrolled hyperphosphatemia with previous phosphorus-lowering therapy.

Hyperphosphatemia has been shown to cause numerous adverse effects, including parathyroid hyperplasia, renal bone disease and arterial calcification, which in turn lead to increased morbidity and mortality [1–3]. Consequently, management of...
serum phosphorus has been an important therapeutic target in patients with kidney disease, and several oral phosphate binders, either calcium-based or non-calcium-based, have been developed and introduced in clinical practice [10, 11]. Because of concerns that calcium overload may exacerbate arterial calcification in the long-term, previous studies have focused on the effect of calcium-based versus non-calcium-based phosphate binders on survival. Our results are consistent with these studies in showing that use of phosphate binders may lead to improved survival. It is, however, important to note that in our study the survival advantage of lanthanum was not evident in patients with controlled hyperphosphatemia, which is in contrast to the previous studies showing a significant, albeit less pronounced, survival benefit of phosphate binders even in patients with well-controlled serum phosphorus levels [26–28]. Although accumulating evidence supports the validity of more aggressive treatment of hyperphosphatemia than before, further work is needed to determine the optimal target level of serum phosphorus and to justify such intensive strategies for controlling hyperphosphatemia.

To our knowledge, only one post hoc analysis of a randomized controlled trial addressed the question of whether the use of lanthanum improves survival [25]; this study demonstrated a 14% reduction in the risk of death in the lanthanum group versus the standard therapy group, but this did not reach statistical significance. However, it should be noted that the control of serum phosphorus was similar in both groups during the study period, which may have resulted in underestimation of the survival benefit of lanthanum. In contrast, addition of lanthanum improved control of serum phosphorus significantly in this study, which enabled us to more accurately capture the effect of lanthanum on survival, particularly by focusing on patients with uncontrolled hyperphosphatemia with previous therapy.

Several recent observational studies have shown a survival benefit for hemodialysis patients treated with phosphate binders versus those who were untreated [26–28]. Our results are consistent with these studies in showing that use of phosphate binders may lead to improved survival. It is, however, important to note that in our study the survival advantage of lanthanum was not evident in patients with controlled hyperphosphatemia, which is in contrast to the previous studies showing a significant, albeit less pronounced, survival benefit of phosphate binders even in patients with well-controlled serum phosphorus levels [26–28]. Although accumulating evidence supports the validity of more aggressive treatment of hyperphosphatemia than before, further work is needed to determine the optimal target level of serum phosphorus and to justify such intensive strategies for controlling hyperphosphatemia.

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There are several possible mechanisms through which lanthanum prescription might have improved survival. The most straightforward mechanism is that improved control of serum phosphorus by adding lanthanum may have attenuated progression of vascular calcification and thereby reduced the risk of cardiovascular morbidity and mortality. This possibility is supported by our findings that the survival advantage of lanthanum was more pronounced among patients with more severe hyperphosphatemia. In addition, amelioration of hyperphosphatemia with lanthanum prescription may have allowed the patient to relax dietary phosphate restriction, which may have led to better nutritional status and thereby improved survival [29]. Another possibility is that the use of lanthanum reduced the need for prescription of calcium-based phosphate binders, which may have resulted in reduced calcium load and...
thereby slowed the progression of vascular calcification. Finally, the survival benefit associated with lanthanum might be in part mediated through the ability of lanthanum to lower serum fibroblast growth factor 23 (FGF23) because a recent clinical and experimental study has identified a pathological effect of FGF23 on cardiomyocytes to induce left ventricular hypertrophy [31].

The major strength of this study was that the observation started immediately before the market introduction of lanthanum in Japan. This enabled us to use covariates that immediately preceded and thus potentially influenced the decision to initiate lanthanum for multivariable adjustment and propensity score calculation. It should also be stressed that in the absence of long-term safety data at the time of market introduction, there were substantial differences between clinicians in the preference for using this new phosphate binder in Japan [32], as highlighted by our observation of less aggressive use and up-titration of the drug. This created a unique situation where a sufficient number of patients were and were not treated with lanthanum even if they had similar baseline characteristics. This situation provided sufficient overlap of the propensity score between the two groups and allowed us to perform matching without marked loss of sample size. Of note, patients receiving dialysis are nearly fully reimbursed by the government in Japan, so it is unlikely that socioeconomic status affected the decision whether or not to use lanthanum for the patient.

This study has several limitations. First, and perhaps most importantly, we did not have information on dietary protein intake. Although we adjusted for several nutritional indicators such as BMI, nPCR and serum albumin, we cannot exclude the possibility that patients in the lanthanum group had higher protein intake than those in the non-lanthanum group.
and this difference was related to the survival advantage for the lanthanum group. Second, we did not have a measure of adherence to phosphate binders. A recent observational study reported a high incidence of non-adherence to lanthanum in the USA [33]; however, we do not believe that this affected our results because non-adherence to lanthanum would tend to bias the survival effect of lanthanum toward the null. Finally, as with all observational studies, our results should not be interpreted as causal. The possibility that residual confounding or selection bias explained our findings cannot be excluded.

In conclusion, this study showed that prescription of lanthanum was associated with a significant survival advantage for hemodialysis patients with uncontrolled hyperphosphatemia. Our results suggest that prescription of lanthanum and the resultant improvement in phosphorus control lead to improved survival. Randomized controlled trials are needed to determine whether management of hyperphosphatemia with lanthanum actually improves survival in maintenance hemodialysis patients.

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CONFLICT OF INTEREST STATEMENT

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(See related article by Block and Isakova. Tip-toeing toward the finish line. Nephrol Dial Transplant 2015; 30: 1–3.)