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Original Investigation

Erythropoiesis-Stimulating Agent Responsiveness and Mortality in Hemodialysis Patients: Results from a Cohort Study From the Dialysis Registry in Japan

Shingo Fukuma, MD,[1] Takuhiro Yamaguchi, PhD,[2] Seiji Hashimoto, MD, PhD,[3] Shigeru Nakai, MD, PhD,[3] Kunitoshi Iseki, MD, PhD,[3] Yoshiharu Tsubakihara, MD, PhD,[3] and Shunichi Fukuhara, MD[1]

Background: Patient responsiveness to erythropoiesis-stimulating agents (ESAs), notoriously difficult to measure, has attracted attention for its association with mortality. We defined categories of ESA responsiveness and attempted to clarify their association with mortality.

Study Design: Cohort study.

Setting & Participants: Data from Japan's dialysis registry (2005-2006), including 95,460 adult hemodialysis patients who received ESAs.

Predictor: We defined 6 categories of ESA responsiveness based on a combination of ESA dosage (low [<6,000 U/wk] or high [≥6,000 U/wk]) and hemoglobin level (low [<10 g/dL], medium [10-11.9 g/dL], or high [≥12 g/dL]), with medium hemoglobin level and low-dose ESA therapy as the reference category.

Outcomes: All-cause and cardiovascular mortality during 1-year follow-up.

Measurements: HRs were estimated using a Cox model for the association between responsiveness categories and mortality, adjusting for potential confounders such as age, sex, postdialysis weight, dialysis duration, comorbid conditions, serum albumin level, and transferrin saturation.

Results: Median ESA dosage (4,500-5,999 U/wk) was used as a cutoff point, and mean hemoglobin level was 10.1 g/dL in our cohort. Of 95,460 patients during follow-up, 7,205 (7.5%) died of all causes, including 5,586 (5.9%) cardiovascular deaths. Low hemoglobin levels and high-dose ESA therapy were both associated with all-cause mortality (adjusted HRs, 1.18 [95% CI, 1.09-1.27] for low hemoglobin level with low-dose ESA and 1.44 [95% CI, 1.34-1.55] for medium hemoglobin level with high-dose ESA). Adjusted HRs for high-dose ESA with low hemoglobin level (hyporesponsiveness) were 1.94 (95% CI, 1.82-2.07) for all-cause and 2.02 (95% CI, 1.88-2.17) for cardiovascular mortality. We also noted the interaction between ESA dosage and hemoglobin level on all-cause mortality (likelihood ratio test, $P = 0.002$).

Limitations: Potential residual confounding from unmeasured factors and single measurement of predictors.

Conclusions: Mortality can be affected by ESA responsiveness, which may include independent and interactive effects of ESA dose and hemoglobin level. Responsiveness category has prognostic importance and clinical relevance in anemia management.

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INDEX WORDS: Erythropoiesis-stimulating agent responsiveness; mortality; hemodialysis.

Erythropoiesis-stimulating agent (ESA) responsiveness has attracted attention for its association with mortality in hemodialysis (HD) patients.[1-3] Responsiveness can vary widely, and hyporesponsiveness in particular is believed to predict poorer outcomes than other conditions. Both high-dose ESA therapy and low hemoglobin levels may contribute to poorer outcomes in patients with ESA hyporesponsiveness.[1,4-6] However, a recent meta-analysis and systematic review[7,8] were unable to determine a recommended hemoglobin level suitable for use in clinical guidelines[9-11] or estimate the independent effects of ESA dose on mortality. In addition, the impact of ESA dose–hemoglobin level interaction on mortality is not precisely understood.

ESA responsiveness is relative, not absolute; the 2 determinants of responsiveness are ESA dose and hemoglobin level. Although previous studies have defined ESA responsiveness based on ESA dose,[1] hematocrit change per increase in ESA dose,[2] or erythropoietin resistance index,[3,12] these indicators are rarely used in practice because physicians commonly adjust ESA dosage according to hemoglobin

From the [1]Department of Epidemiology and Healthcare Research, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan; [2]Biostatistics, Tohoku University Graduate School of Medicine, Sendai; and [3]Committee of Renal Data Registry of the Japanese Society for Dialysis Therapy, Tokyo, Japan.

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Address correspondence to Shingo Fukuma, MD, Department of Epidemiology and Healthcare Research, Graduate School of Medicine and Public Health, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: s.fukuma@ft4.ecs.kyoto-u.ac.jp

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level (or hematocrit), and the association between ESA dose and hemoglobin level is not linear. The National Kidney Foundation– KDOQI (Kidney Disease Outcomes Quality Initiative) and European guidelines define ESA hyporesponsiveness as failing to achieve target hemoglobin levels while receiving an ESA dosage >500 U/kg/wk.[9,10] However, given that the mean ESA dosage in Japan is less than one third that in the United States,[13] whether the association between ESA responsiveness and mortality is similar for lower ESA dosages is uncertain.

We attempted to clarify the impact of ESA responsiveness, including the effects of ESA dose and hemoglobin level, on mortality. We defined ESA responsiveness categories by combining ESA dose and hemoglobin level and then examined the association between category and mortality at 1 year in a large cohort using Japan's nationwide dialysis registry.

METHODS

Study Population and Data Source

This cohort study included HD patients who were older than 20 years, had spent at least 3 months on HD therapy, received ESAs, and had available data for hemoglobin levels. We excluded patients with multiple myeloma and polycystic kidney disease because previous studies have reported that response to ESAs differs between these patients and others.[14,15] We also excluded patients with acute cardiovascular disease (CVD) at baseline because they confound the association between ESA responsiveness and mortality. Ultimately, 95,460 enrolled patients were analyzed.

Data were obtained from the nationwide dialysis registry of the Japanese Society for Dialysis Therapy, a database that contains data for large numbers of HD patients in Japan, including demographic information (eg, age, sex, time on dialysis therapy, primary cause of end-stage renal disease, diabetes, history of CVD, postdialysis body weight, and weekly ESA dosage) and clinical data (eg, hemoglobin, serum albumin, C-reactive protein [CRP], transferrin saturation, and ferritin). The precise design of the dialysis registry has been described previously.[16] We used standard analysis file coded as JRDR-08005. Baseline demographic data for all patients were collected from the database in December 2005. All ESAs used in the present study were epoetin α or epoetin β, and ESA dosage was reported as categorical data (units/week; <1,500, 1,500-2,999, 3,000-4,499, 4,500-5,999, 6,000-8,999, or ≥9,000). Data regarding route and frequency of ESA administration were not documented in the registry. Mortality data (time and cause) were collected from the database between December 2005 and December 2006 (follow-up, 1-12 months).

Definition of Exposure: ESA Responsiveness

We defined ESA dosage as 2 categories (<6,000 or ≥6,000 U/wk) according to the median values in our cohort (4,500-5,999 U/wk) and hemoglobin level as 3 categories (<10, 10-11.9 or ≥12 g/dL) according to clinical guidelines.[11] ESA responsiveness thus was allotted to 6 categories combining the categorical determinants of ESA dosage (2 groups) and hemoglobin level (3 groups). We combined the 2 categorical variables and used them as exposure categories to evaluate the biological interaction between ESA dosage and hemoglobin level. We also defined 12 categories of ESA responsiveness based on narrower categories of ESA dosage (<3,000, 3,000-5,999, 6,000-8,999, or ≥9,000 U/wk) and categories of hemoglobin level (<10, 10-11.9, or ≥12 g/dL) to examine a dose-dependent association.

Outcomes

The primary outcome was all-cause mortality rate, and the secondary outcome was cardiovascular mortality rate. *International Classification of Diseases, 10th Revision* codes were used to define cardiovascular mortality (codes I10-I79). Cardiovascular death included sudden death; death from heart failure, myocardial infarction, or stroke; and death from other vascular disease.

Statistical Analysis

Exploratory multivariable logistic regression analysis was performed to determine which factors may be used to predict ESA-hyporesponsive patients. We defined ESA hyporesponsiveness as having hemoglobin level <10 g/dL while receiving an ESA dosage ≥6,000 U/wk. The model included all potential risk factors, such as age, sex, time on dialysis therapy, history of CVD, diabetes, postdialysis body weight, transferrin saturation, and CRP and serum albumin levels. Odds ratios and their 95% confidence intervals (CIs) were estimated.

For each category of ESA responsiveness, we calculated mortality rate and 95% CIs for all-cause and CVD-associated mortality at 1 year. We conducted Cox proportional regression analysis to estimate hazard ratios (HRs) and their 95% CIs for the association between categories of ESA responsiveness and mortality for all-cause and CVD-associated mortality. Patients who underwent transplant or changed modalities were treated as censored.

Categories of ESA responsiveness were included in models by creating multiple dichotomous variables. Patients with hemoglobin levels of 10-11.9 g/dL receiving an ESA dosage <6,000 U/wk were our reference category because evidence suggests that this category has the lowest mortality risk.[2] For Cox regression, our model included adjustment for age, sex, time on dialysis therapy, postdialysis body weight, history of CVD, diabetes, serum albumin level, and transferrin saturation. Given that previous studies found these covariates to be potential confounding factors,[1-3,5] we also examined a model including these factors with ferritin level, CRP level, single-pool Kt/V, and normalized protein nitrogen appearance. Each variable in the model was checked and log transformation or construction of categorical variables was used when appropriate. We assessed the statistical interaction between ESA dosage and hemoglobin level using the likelihood ratio test comparing the Cox model with and without the product terms. We also assessed the biological interaction between high-dose ESA therapy and low hemoglobin level calculating the relative excess risk due to interaction (RERI). We calculated RERI using adjusted HRs for all-cause mortality.[17,18] If there is no biological interaction, RERI is equal to 0.

We also defined 12 categories of ESA responsiveness that have narrower categories of ESA dosage, and used Cox regression analysis to examine whether the association between ESA dosage and mortality was dose dependent across hemoglobin levels. Patients with hemoglobin levels <10 g/dL and ESA dosage <3,000 U/wk were used as the reference category.

We also performed subgroup analysis according to transferrin saturation (<20% or ≥20%), ferritin level (<200 or ≥200 ng/mL), and age (<65 or ≥65 years). The cutoff points for these factors were defined according to clinical guidelines.[11] We used Cox regression analysis to examine whether the association between ESA responsiveness and mortality was consistent within these subgroups.

A multiple imputation approach using chained equations was used to account for missing covariates. Results were similar to those obtained on complete set analysis.