Original article

Effect of anemia correction to the modestly high hemoglobin level in patients with chronic kidney disease on left ventricular hypertrophy

Makoto Akaishi (MD, PhD, FJCC) [a,*], Michiaki Hiroe (MD, PhD, FJCC) [b], Yoshiyuki Hada (MD, PhD, FJCC) [c], Makoto Suzuki (MD, FJCC) [d], Yoshiharu Tsubakihara (MD, PhD) [e], Tadao Akizawa (MD, PhD) [f], KRN321 Study Group

[a] Department of Cardiology, Kitasato University Kitasato Institute Hospital, Tokyo, Japan
[b] Cardiology Division, National Center for Global Health and Medicine, Tokyo, Japan
[c] Department of Cardiology, Sakakibara Memorial Clinic, Tokyo, Japan
[d] Department of Clinical Laboratory, Toho University Medical Center Ohashi Hospital, Tokyo, Japan
[e] Department of Comprehensive Kidney Disease Research, Osaka University Graduate School of Medicine, Osaka, Japan
[f] Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

ABSTRACT

Background and purpose: To assess effects of long-term anemia management on left ventricular hypertrophy in patients with chronic kidney disease (CKD) not on dialysis, we performed secondary outcome analyses of a randomized controlled study that evaluated effects of anemia management with erythropoiesis stimulating agents in this population.
Methods and subjects: Subjects [hemoglobin (Hb) < 10.0 g/dL, $2.0 \le$ serum creatinine < 6.0 mg/dL] were randomized either to high Hb ($11.0 \le$ target Hb ≤ 13.0 g/dL with darbepoetin alfa), or to low Hb group ($9.0 \le$ target Hb ≤ 11.0 g/dL with recombinant human erythropoietin), and followed up to 48 weeks. Data from echocardiographic evaluation and values of neurohumoral factors associated with heart failure were assessed in subjects whose data were evaluable both at the baseline and at the end point.
Results: The high Hb group achieved target range Hb levels (12.1 ± 1.1 g/dL, at 32 weeks, $N = 111$), which was significantly higher ($p < 0.001$) than the low Hb group ($N = 95$). Though blood pressure and renal function changes were similar between the groups, left ventricular diastolic dimension was significantly decreased only in the high Hb group ($p < 0.001$), and the change in left ventricular mass index (LVMI) correlated coarsely but significantly with the achieved Hb levels ($r = 0.147$, $p = 0.032$). The higher Hb levels were associated with greater reduction in LVMI and left ventricular wall thickness, and the lower Hb levels with the greater increase in human arterial- or brain natriuretic polypeptide levels.
Conclusions: Anemia correction targeting modestly higher Hb levels better preserves cardiac function in CKD patients not on dialysis.

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Introduction

Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease (CVD), and the risk of CVD increases as glomerular filtration rate (GFR) decreases. A prospective analysis showed that CKD is a significant risk factor for CVD also in the general Japanese population [1–3]. Furthermore, CKD patients with anemia are at a greater risk of developing CVD. Observational studies revealed that anemia or left ventricular hypertrophy

(LVH) associated with CKD is an additional risk for CKD and total mortality [4,5]. Cardio-renal anemia syndrome (CRA syndrome) is another complication, in which CKD, chronic heart failure (CHF), and anemia can cause or be caused by the others, or act as risk factors for each other [6,7]. As CKD progresses, the patients may develop anemia. If appropriate anemia management breaks the vicious cycle of CRA syndrome, the progression of each disease can be prevented. Approximately 75% of CKD patients are complicated with LVH at the initiation of renal replacement therapy, and have various complications of CVD such as CHF, coronary artery disease, or peripheral vascular disease [8–10]. The importance of anemia management from the early stages of CKD has been emphasized and several controlled studies have been conducted to determine the reasonable target levels in correcting anemia [11–15]. However, the optimal target levels for

* Corresponding author at: Department of Cardiology, Kitasato University Kitasato Institute Hospital, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan. Tel.: +81 03 3444 6161; fax: +81 03 3448 0553.
E-mail address: akaishim@insti.kitasato-u.ac.jp (M. Akaishi).

anemia correction remain controversial in regard to reducing the risk of developing CVD and improving the prognosis in CKD patients.

In Japan, recombinant human erythropoietin (rHuEPO) has been used in clinical settings since 1990. Because periodic erythrocyte transfusion was the only therapeutic choice for CKD patients with anemia before the introduction of rHuEPO, anemia correction with rHuEPO dramatically decreased the number of CKD patients requiring erythrocyte transfusion and greatly improved patients' quality of life, as well as their prognosis. The hemoglobin (Hb) levels for anemia correction with rHuEPO at around 10 g/dL have been recommended. However, in a late phase II clinical study of darbepoetin alpha, LVH and myocardial stress were significantly reduced in CKD patients not on dialysis whose Hb levels were increased to greater than 11.0 g/dL in16 weeks [16,17]. In the present study, we further analyzed the secondary outcomes of a 48-week, randomized, controlled study [17] to determine whether maintaining target hemoglobin (Hb) levels higher than those achieved by conventional anemia treatment levels ($11.0 \leq Hb \leq 13.0$ g/dL and $9.0 \leq Hb \leq 11.0$ g/dL, respectively) beneficially affects LVH and cardiac overload in patients with CKD not on dialysis.

Methods

Study design and patients

The present study is a sub-analysis focused on cardiac functions in study subjects of a multicenter open-label randomized controlled study involving 79 medical centers conducted between November 2005 and April 2007 [17]. In subsets of the study population that were followed up for 48 weeks, data regarding cardiac functions were assessed in the present study comparing values at baseline and at 32 weeks after starting erythropoiesis stimulating agent (ESA: darbepoietin alfa or rHuEPO) treatment.

The protocol of the main study was approved by institutional review boards of all the participating medical centers. All the participants in the study gave written informed consent.

The detailed protocol of the study was described elsewhere [17], and a brief summary of the protocol is presented here.

The study included patients with CKD not on dialysis, whose Hb levels were less than 10.0 g/dL, and whose serum creatinine (Cr) levels were ≥ 2.0 mg/dL and <6.0 mg/dL or creatinine clearance (Ccr) levels ≤ 30.0 mL/min.

The enrolled patients were randomized to either of the two treatment groups: the high Hb group, in which darbepoetin alfa was administered to achieve a target Hb level of ≥ 11.0 g/dL and ≤ 13.0 g/dL, or the low Hb group, in which rHuEPO was administered to reach a target Hb level of ≥ 9.0 g/dL and ≤ 11.0 g/dL. Randomization was performed using the minimization method with Hb levels (<9.0 g/dL or ≥ 9.0 g/dL), serum Cr levels (<4.0 mg/dL or ≥ 4.0 mg/dL), and the presence or absence of diabetes mellitus, and participating medical centers as adjustment factors.

Subjects in the high Hb group started with subcutaneous darbepoetin alfa 60 μg every two weeks. After reaching the target Hb level ($11.0 \leq Hb \leq 13.0$ g/dL), the Hb level was maintained with subcutaneous darbepoetin alpha every 2 or 4 weeks. Subjects in the low Hb group started to receive subcutaneous rHuEPO at a dose of 6000 IU once a week, in accordance with the dosage and administration approved in Japan. After reaching the target Hb level ($9.0 \leq Hb \leq 11.0$ g/dL), the Hb level was maintained with subcutaneous rHuEPO once a week or every 2 weeks for 48 weeks. During the study, a combination of supplemental iron as necessary, blood pressure control, and dietary control for salt and protein intake were also administered as described in detail elsewhere [17].

Measurement of cardiac function and other examinations

Echocardiography, assay for neurohumoral factors [serum human brain natriuretic peptide (BNP) and human atrial natriuretic peptide (hANP)], and chest X-ray were performed to evaluate cardiac function at baseline and 32 weeks or at discontinuation of the treatment. Blood pressure, heart rate, complete blood cell counts, and blood chemistry were assessed every 2 or 4 weeks depending on the injection schedule of darbepoetin alpha or rHuEPO.

Since M-mode imaging was necessary for echocardiographic measurements, the following patients with factors that might hamper appropriate image acquisition and/or its evaluation were excluded.

Those who discontinued the study earlier than 16 weeks after the start of treatment were also excluded from the evaluation.

(1) Patients with pericardial disease or myocarditis.
(2) Patients with multiple ventricular premature contractions.
(3) Patients with atrial fibrillation.
(4) Patients with myocardial infarction.
(5) Patients with organic valvular disease or with moderate to severe valvular regurgitation.
(6) Patients with hypertrophic cardiomyopathy.
(7) Patients with arteriovenous fistula.

At each medical center, the following five types of echocardiograms were obtained: left ventricular M-mode echocardiogram and the end-diastolic/end-systolic long and short axis cross-sectional images of the left ventricle, and all the images were collected and evaluated by an external evaluation committee consisting of 3 cardiologists. Two cardiologists first evaluated the quality of echocardiograms, and then measured left ventricular end diastolic dimension (LVDd), left ventricular end systolic dimension (LVDs), interventricular septal thickness (IVST), and posterior wall thickness (PWT) by left ventricular M-mode echocardiography using the ASE method (American Society of Echocardiography leading edge recommendations) [18]. The mean value of the measurement results by two cardiologists was used as the final measurement value. When the two measurements disagree, the results were discussed with a third cardiologist and the final decision reflected the consensus of all three cardiologists. In order to avoid bias, all evaluations and measurements were conducted after masking the treatment groups, the timing of examinations, and patient characteristics.

From the measured left ventricular parameters, left ventricular mass was calculated using Devereux's formula [19]: $0.8 \times \{1.04 \times [(LVDd + IVST + PWT)^3 - LVDd^3]\} + 0.6$, which was divided by body surface area to obtain LVMI. To assess left ventricular systolic function, left ventricular ejection fraction (LVEF) was calculated using left ventricular volume by the Teichholz method.

Analyses

Patient characteristics

Summary statistics were obtained and compared by two-sample t-test for continuous variables and by χ^2 test for frequencies of nominal variables.

Comparison of cardiac function indices between the high- and low-Hb groups

Cardiac function was analyzed in patients whose echocardiograms were obtained and evaluable both before and after the