Daimon et al. Renal Replacement Therapy (2016) 2:58
DOI 10.1186/s41100-016-0071-x

Renal Replacement Therapy

RESEARCH Open Access

# Influence of continuous erythropoietin receptor activator (CERA) administration intervals on erythropoietic effect in hemodialysis patients

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## Abstract

**Background:** Erythropoietin deficiency is the major cause of anemia in hemodialysis patients. Although continuous erythropoietin receptor activator (CERA) has a long half-life and once-monthly administration is recommended, the optimal interval to achieve the greatest efficacy is not known.

**Methods:** In 44 hemodialysis patients, CERA was administered at an interval of once every 2 weeks (Q2W) and 4 weeks (Q4W) consecutively and reticulocyte counts and hemoglobin levels were compared prospectively. In six patients with CERA 100 μg/4 weeks, CERA intervals were further changed to 1 week (Q1W).

**Results:** Mean reticulocyte counts were higher during Q2W than Q4W (41.5 ± 10.7 and 36.4 ± 8.8 × $10^3$/μL, respectively, $p < 0.0001$), and hemoglobin levels decreased during Q4W. These results were irrespective of the CERA dose (50, 100, and 150 μg/4 weeks). In six patients with CERA 100 μg/4 weeks, although not significant, reticulocyte counts were higher during Q2W and Q1W than Q4W and hemoglobin levels were highest during Q1W ($p < 0.05$).

**Conclusions:** In our hemodialysis patients, an interval of CERA shorter than 4 weeks appeared to be more effective for the treatment of anemia.

**Keywords:** CERA, Interval, Reticulocyte, Hemoglobin

## Background

Anemia is common in patients with chronic renal failure. Its causes include erythropoietin (EPO) deficiency, iron deficiency, inflammation, hyperparathyroidism, and in hemodialysis patients, blood loss related to the hemodialysis procedure. Although all these factors contribute to the anemia of hemodialysis patients, EPO deficiency is thought to be the major one. Anemia is associated with poorer patient survival [1, 2] and quality of life [3]. After the introduction of erythropoietin-stimulating agents (ESAs), the management of renal anemia has improved and has been associated with improved survival of hemodialysis patients [4].

Traditional ESAs have relatively short intravenous half-lives (epoetin alfa and beta, 7–9 h) [5] and require frequent administration. Continuous erythropoietin receptor activator (CERA) has a long half-life (134 and 139 h following intravenous and subcutaneous administration, respectively) [6] and is administered at wider intervals than epoetin or darbepoetin alfa for renal anemia in patients with chronic kidney disease. Although conversion to CERA with intervals of once every 2 weeks (Q2W) or 4 weeks (Q4W) from other ESAs is achieved safely in hemodialysis patients and once-monthly administration is recommended in Japan, the optimal interval of CERA administration is not known. Recently, it is reported that more continuous erythropoiesis was achieved with a Q2W administration of CERA than Q4W [7], and Q2W administration of CERA is more effective than Q4W to achieve target hemoglobin (Hb) levels [8]. Although we also reported more effective

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erythropoiesis of CERA by Q2W than Q4W, the fluctuation of Hb levels during Q4W is greater than that during Q2W [9], which makes it difficult to compare the true effect of the interval of CERA administration on Hb levels.

Usually the responsiveness to ESAs in hemodialysis patients is defined by the ESA dose and Hb levels [10], with low Hb levels at the same dose of ESAs meaning hypo-responsiveness to ESAs. This "responsiveness" is not equal to "red blood cell (RBC) production". In the absence of considerable blood loss, Hb levels are affected not only by the RBC production rate but also by the death rate, which means RBC lifespan. In hemodialysis patients, shortened and high interindividual variability of RBC lifespan is reported [11] and may have a substantial impact on Hb levels, which has been largely neglected.

For these reasons, Hb levels alone are not suitable to evaluate the erythropoietic effect of CERA according to administration interval, which prompted us to compare also reticulocyte counts during 4-, 2-, and 1-week intervals of CERA administration.

## Methods

This prospective study focused on 44 hemodialysis patients in Daimon Clinic for Internal Medicine, Nephrology and Dialysis, whose Hb levels were controlled between 9 and 12 g/dL without changes in the CERA dose administered by Q2W for more than 3 months. Table 1 shows patient characteristics at baseline. Hb was controlled within a narrow range (10.9 ± 0.8 g/dL) under the same dosage of CERA administered by Q2W (50 μg per 4 weeks, $N = 25$; 100 μg, $N = 13$; and 150 μg, $N = 6$). Serum levels of hepcidin-25 were measured using a liquid chromatography-tandem mass spectrometric method [12]. Reticulocyte counts and Hb levels were evaluated every week for 4 weeks, and then CERA administration intervals were changed to 4 weeks (same dosage per 4 weeks). After the 4-week wash-out period, weekly reticulocyte counts and Hb levels were evaluated again for 4 weeks. To compare the erythropoietic effect of CERA by Q2W and Q4W, we evaluated the mean reticulocyte counts of the first hemodialysis session of the week during the 4 weeks of the evaluation period.

In 6 of 13 patients, 100 μg of CERA was administered every 4 weeks and Hb levels were between 9 and 12 g/dL at the end of the above study, after which CERA intervals were further changed to 1 week (Q1W) (25 μg of CERA every week) and reticulocyte counts and Hb levels were evaluated prospectively for a further 8 weeks (Fig. 1).

As a rule, iron has been administered orally in our clinic, with intravenous iron not administered during the study period. In 28 of the 44 patients, oral iron had been prescribed every day at least 3 months before the study (sodium ferrous citrate, $N = 21$; ferric citrate, $N = 7$, respectively) and did not change during the study period.

This study was approved by the local ethics committee (issue 2014-A1 at Daimon Clinic for Internal Medicine, Nephrology and Dialysis), and written informed consent was obtained from all patients.

### Statistical analyses

Data were expressed as the mean ± SD. Paired and unpaired $t$ tests and chi square test were used to compare the data. Statistical significance is defined as $p$ less than 0.05.

## Results

Figure 2 shows the weekly changes of reticulocyte counts during CERA administration by Q2W and Q4W. Three groups by CERA dose (50, 100, and 150 μg/4W) showed a similar pattern of reticulocyte count changes. As shown in Table 2, mean reticulocyte counts were higher during Q2W than during Q4W irrespective of CERA dose ($p < 0.005$, $p < 0.05$, and $p < 0.05$ for CERA 50, 100, and 150 μg/4W, respectively). Although Hb levels were stable during the period of CERA by Q2W, after the switch to Q4W, Hb levels showed a tendency to decrease (Fig. 3).

In six patients with CERA 100 μg per 4 weeks who were switched to Q1W further, as shown in Fig. 4, reticulocyte counts were maximal ($50–56 \times 10^3/\mu L$) around 2 weeks after the switch to Q1W and Hb increased gradually and reached a plateau 6 weeks after the switch to Q1W. Mean reticulocyte counts during the evaluation periods of Q4W, Q2W, and Q1W were 34.6 ± 22.3, 41.9 ± 19.9, and 38.3 ± 10.8 × $10^3/\mu L$, respectively ($p$ = n.s.). Mean Hb levels were 11.1 ± 0.9, 11.2 ± 1.3, and 12.0 ± 2.2 g/dL, respectively ($p < 0.05$ Q1W vs. Q2W and Q1W vs. Q4W). Serum iron and ferritin levels at the switch to Q1W were 105.3 ± 42.5 μg/dL and 145.3 ± 81.5 ng/mL, and 8 weeks later, 75.3 ± 40.9 μg/dL ($p$ = n.s.) and 91.6 ± 109.6 ng/mL ($p < 0.05$), respectively.

## Discussion

EPO deficiency is the major cause of anemia in patients with chronic renal failure. ESAs correct anemia by binding to erythropoietin receptors expressed on progenitor cells in the bone marrow which leads to inhibition of cell apoptosis and enhancement of proliferation and differentiation [13]. The stimulated progenitor cells differentiate to erythroblasts, then mature to reticulocytes and finally to RBCs. Hematopoiesis by ESA administration influences iron metabolism. Although the precise mechanisms are not clear, in hemodialysis patients, ESA administration exerts a biphasic pattern of serum hepcidin-25 levels; early upregulation followed by late downregulation [14], and low serum hepcidin levels

**Table 1** Patient characteristics at baseline

| CERA dosage (μg/4 weeks) | Male (%) | Age (years) | Diabetes (%) | HD vintage (months) | BUN (mg/dL) | Cr (mg/dL) | TP (g/dL) | Alb (g/dL) | Hb (g/dL) | CRP (mg/dL) | Fe (μg/dL) | Ferritin (ng/mL) | Hepcidin-25 (ng/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 50 (*N* = 25) | 16 (64.0) | 70.0 ± 11.3 (35–87) | 13 (52.0) | 105.5 ± 90.6 | 62.6 ± 13.6 | 10.7 ± 2.1 | 6.5 ± 0.5 | 3.8 ± 0.3 | 10.9 ± 0.8 | 0.35 ± 0.53 | 79.7 ± 26.0 (36–123) | 143.2 ± 155.0 (16.1–824) | 74.2 ± 41.9 (0.4–175.9) |
| 100 (*N* = 13) | 9 (69.2) | 70.6 ± 7.7 (53–85) | 4 (30.8) | 67.4 ± 66.4 | 67.5 ± 14.2 | 10.4 ± 1.9 | 6.7 ± 0.3 | 3.7 ± 0.3 | 11.0 ± 0.7 | 0.25 ± 0.52 | 82.1 ± 31.7 (32–145) | 89.1 ± 70.4 (25.1–233) | 38.9 ± 33.6 (0.2–122) |
| 150 (*N* = 6) | 5 (83.3) | 69.0 ± 9.3 (51–75) | 5 (83.3) | 88.5 ± 45.4 | 57.9 ± 23.2 | 9.1 ± 4.0 | 6.6 ± 0.4 | 3.3 ± 0.2 | 10.4 ± 1.0 | 2.46 ± 3.17 | 44.8 ± 15.8 (26–68) | 128.6 ± 89.6 (54.6–263) | 90.2 ± 29.3 (55.7–137.1) |
| All (*N* = 44) | 30 (68.2) | 70.0 ± 9.9 (35–87) | 22 (50.0) | 91.9 ± 79.6 | 63.4 ± 15.2 | 10.4 ± 2.4 | 6.6 ± 0.4 | 3.7 ± 0.3 | 10.9 ± 0.8 | 0.61 ± 1.40 | 75.6 ± 29.0 (26–145) | 125.2 ± 127.7 (16.1–824) | 66.0 ± 41.7 (0.2–175.9) |

Variables are represented as mean ± standard deviation

*HD* hemodialysis, *BUN* blood urea nitrogen, *Cr* creatinine, *TP* total protein, *Alb* albumin, *Hb* hemoglobin, *CRP* C-reactive protein, *Fe* iron

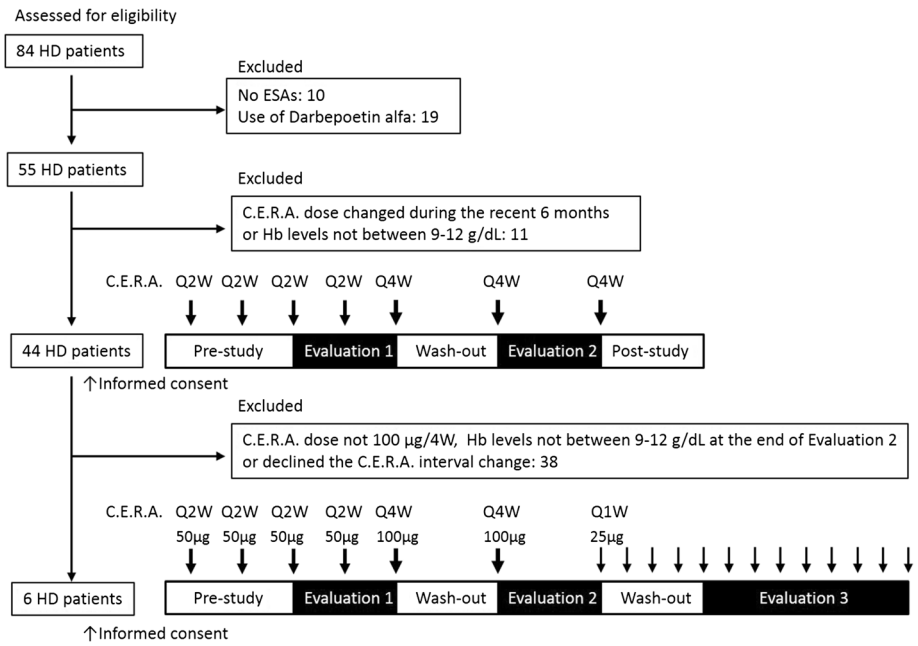


**Fig. 1** Study design schema

facilitate iron utilization, which results in a decrease of serum ferritin levels. The degree of iron utilization and recruitment to the hematopoietic system seems to differ according to the type of ESAs [14–16] and interval of dosing [7, 8]. Transient reduction of serum hepcidin and ferritin levels induced by CERA administration reach a maximum around 1 week after dosing and return to pre-administration levels by 4 weeks, with this being the rationale of the once-monthly administration of CERA. These transient changes of serum ferritin and hepcidin levels induced by CERA are considered to be due to sustained stimulation of erythropoiesis by CERA which lasts

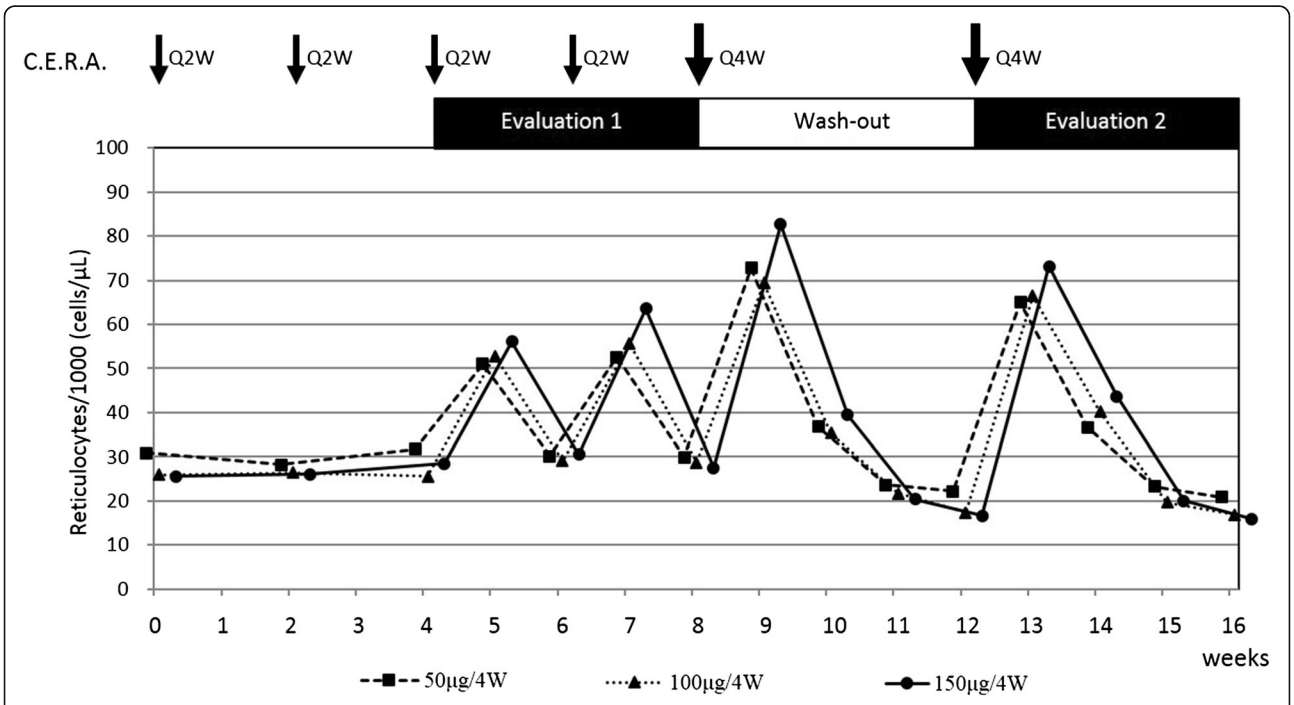


**Fig. 2** Reticulocyte counts according to the dosage of CERA

**Table 2** Mean reticulocyte counts during the administration of CERA by Q2W and Q4W

| CERA dosage (μg/4 weeks) | Q2W/1000 (cells/μL) | Q4W/1000 (cells/μL) | *p* value |
|---|---|---|---|
| 50 (*N* = 25) | 40.7 ± 10.0 | 36.2 ± 9.9 | <0.005 |
| 100 (*N* = 13) | 41.6 ± 12.5 | 35.8 ± 7.8 | <0.05 |
| 150 (*N* = 6) | 44.7 ± 10.8 | 38.4 ± 7.0 | <0.05 |
| All (*N* = 44) | 41.5 ± 10.7 | 36.4 ± 8.8 | <0.0001 |

Variables are represented as mean ± standard deviation

much longer than that induced by epoetin. Although CERA has a long half-life, and once-monthly administration of CERA is safe and reported to save up to 144 injections per hemodialysis patient per year compared with three times weekly dosing [17], it is reported that Q2W administration of CERA is more effective than Q4W to achieve target Hb levels [7, 8, 17], which made us wonder what would be the optimal interval of CERA administration from the standpoint of efficacy.

As shown in Table 2, our study demonstrated higher mean reticulocyte counts in patients with CERA administered at Q2W than Q4W. In six patients, we further evaluated Hb levels and reticulocyte counts after CERA was administered by Q2W, Q4W, and Q1W sequentially (Fig. 4). During Q1W, Hb increased gradually and reached a higher level than that during Q2W and Q4W. Reticulocyte counts were highest in the first 2–4 weeks during the period of Q1W and persisted around the same levels as those of Q2W. Although timing effect of CERA administration on serum iron and ferritin levels must be taken into consideration, decrease of serum iron and ferritin levels during Q1W may indicate more effective iron recruitment for erythropoiesis than Q4W. Although the number of patients on Q1W was very small, this result suggests that not only Q2W but also Q1W administration of CERA has a greater erythropoietic effect than Q4W, and Q1W may have more potential to increase Hb levels than Q2W.

For the production of RBCs, erythropoietin is mandatory, since otherwise erythroid progenitor cells are rapidly lost to apoptosis [18]. Although CERA has a longer half-life than traditional ESAs, our results suggest that 4 weeks as a CERA administration interval is too long to achieve sustained erythropoiesis, and it is anticipated that the longer the interval of CERA administration is, the more erythroid progenitor cells might be lost to apoptosis, resulting in a decrease in the RBC production rate.

We evaluated the erythropoietic effect of CERA administered at different intervals by comparing reticulocyte counts and Hb levels. For this purpose, the CERA dose had to be kept stable during the study period. But it is sometimes difficult to maintain Hb levels within the target ranges without changing the dose of CERA for a substantial period, which meant that the study period had to be rather short. Especially when the CERA interval changes, Hb levels become unstable, and so as the wash-out period of

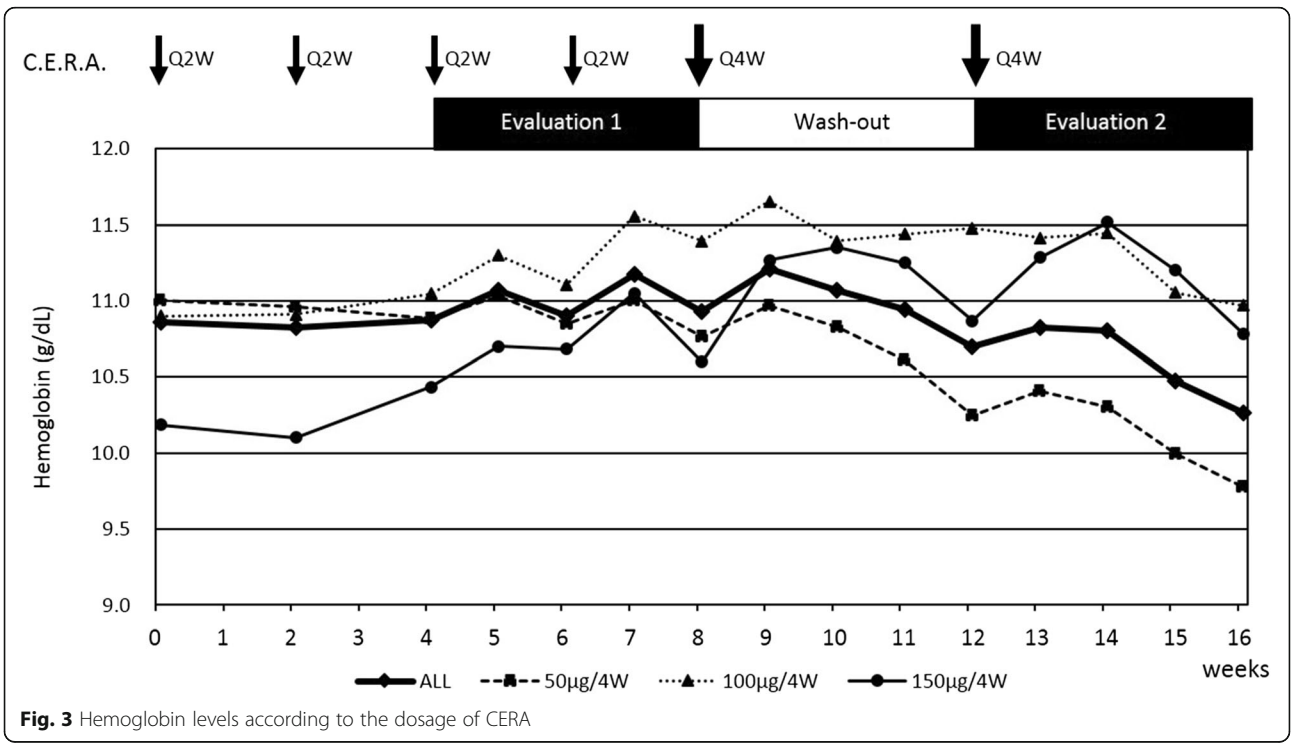


**Fig. 3** Hemoglobin levels according to the dosage of CERA

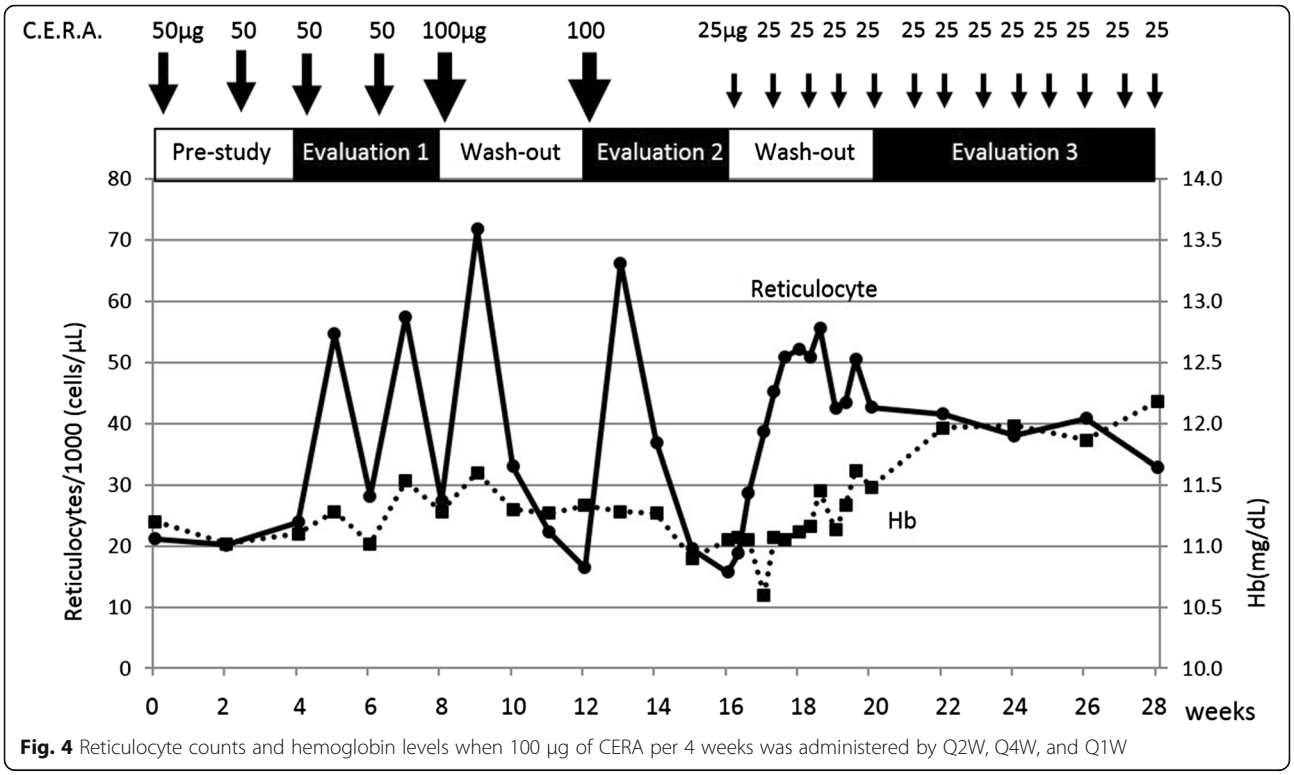


**Fig. 4** Reticulocyte counts and hemoglobin levels when 100 μg of CERA per 4 weeks was administered by Q2W, Q4W, and Q1W

evaluation of CERA administration, we adopted only 4 weeks provisionally. As shown in Fig. 5, which illustrates the changes of reticulocyte counts and Hb levels during 100 μg of CERA, as Q4W was missed (this patient was excluded from evaluation in this study), reticulocyte counts decreased to minimal values at 4 weeks after the administration of CERA and persisted at the same level until the next administration of CERA. Although this is just a single observational datum, this example suggests that the

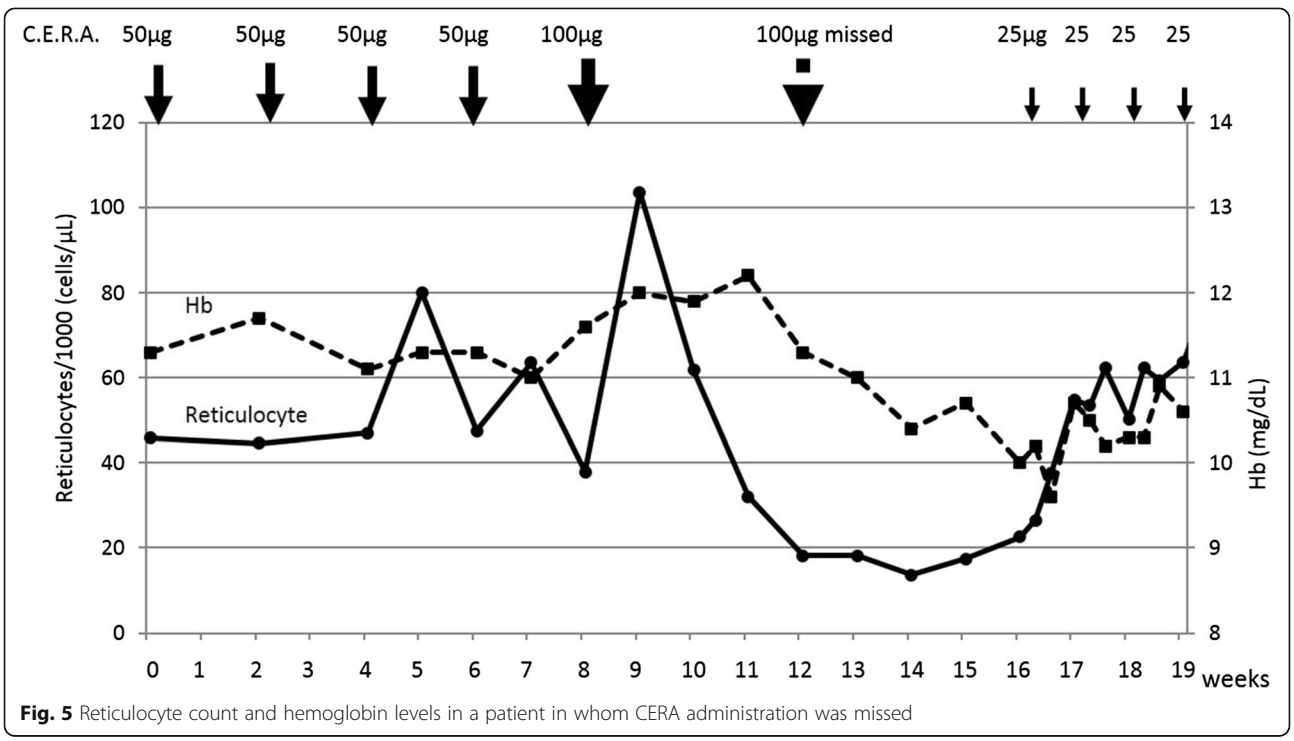


**Fig. 5** Reticulocyte count and hemoglobin levels in a patient in whom CERA administration was missed

erythropoietic effect of CERA is not sustained for more than 4 weeks. This is in accordance with the reports of reticulocyte dynamics in hemodialysis patients treated with CERA [15, 19].

To compare the Hb levels of hemodialysis patients with CERA administered by different intervals, as we reported elsewhere [9], we need to consider the fluctuation patterns of Hb levels, which differ according to the CERA interval. Reticulocyte counts were maximal at 7–10 days of CERA administration and returned to the same levels by the next monthly CERA administration [15, 19], which influenced Hb levels. As a result, not only reticulocyte counts but also Hb levels differ according to the timing of the CERA administration and bloodwork, with the timing effect more prominent when CERA administration intervals are longer. This is also the case when we evaluate the serum iron, ferritin, or hepcidin levels which change in a mirror-image manner to the reticulocyte counts [7, 9, 15, 19].

In this study, Hb levels in the three groups of patients with CERA at doses of 50, 100, and 150 μg per 4 weeks were the same, which means that as a whole patients in the group with smaller dose of CERA have a higher responsiveness to CERA than patients in the group with a larger dose. But this "responsiveness" to ESAs is not equivalent to the "RBC production rate" by ESAs. The anemia of hemodialysis patients is not exclusively attributable to hypoproduction of RBCs. In the absence of considerable blood loss due to hemorrhage or the hemodialysis procedure itself, Hb levels of hemodialysis patients are affected by a shortened RBC lifespan. In healthy adults, the RBC lifespan is about 120 days within a narrow distribution. On the other hand, it is reported that in hemodialysis patients, the mean RBC lifespan is 89 days with high interindividual variability [11]. Although the influence of RBC lifespan on Hb levels in hemodialysis patients is substantial, this factor has been largely neglected [20]. In hemodialysis patients, RBC lifespan is influenced by the uremic state [21, 22], ESA administration [19, 23], and/or inflammation. The higher levels of CRP and hepcidin and lower levels of iron in patients receiving CERA 150 μg/4W than in those receiving 100 or 50 μg/4W may indicate the bluntness of iron recruitment for erythropoiesis but may also indicate a shorter RBC lifespan in patients requiring higher doses of CERA. Also, the highest level of Hb seen during evaluation 3 as compared to that during evaluation 1 and 2 with the same reticulocyte counts may suggest a longer RBC lifespan during Q1W of CERA than that during Q2W and Q4W.

For the effective treatment of anemia in hemodialysis patients, we need to consider multiple factors such as iron deficiency, inflammation, hyperparathyroidism, and dialysis dose and adjust them whenever possible. Also our study suggests that by changing the interval of CERA, the CERA dose can be reduced without exacerbating Hb control. Moreover, it is anticipated that the more sustained erythropoiesis and RBC production associated with a shorter interval of CERA can prevent the occurrence of Hb overshoot or Hb cycling. Although any effects of such factors on the mortality of hemodialysis patients have not been well documented [24], a shorter interval of CERA administration has advantages in stabilizing Hb levels, reducing the cost of ESAs, and reducing the workload associated with frequent changes of the ESA dose.

## Conclusions

In hemodialysis patients, a shorter interval of CERA administration can produce more RBC and increase Hb levels. To achieve efficient and sustained RBC production and maintenance of Hb levels within the narrow target range, shorter than a 4-week interval of CERA administration appears preferable.

#### Abbreviations

CERA: Continuous erythropoietin receptor activator; EPO: Erythropoietin; ESA: Erythropoietin-stimulating agent; Q2W: Once every 2 weeks; Hb: Hemoglobin; RBC: Red blood cell

#### Acknowledgements

The authors thank all staff members working at Daimon Clinic for Internal Medicine, Nephrology and Dialysis.

#### Funding

This study was not supported by any grants or funding.

#### Availability of data and materials

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

#### Authors' contributions

HN, KK, YS, and FK participated in the design of the study. MK conceived of the study and participated in its design. SD was responsible for the research idea and study. All authors read and approved the final manuscript.

#### Competing interests

The authors declare that they have no competing interests.

#### Consent for publication

Not applicable

#### Ethics approval and consent to participate

This study was approved by the local ethics committee (issue 2014-A1 at Daimon Clinic for Internal Medicine, Nephrology and Dialysis), and written informed consent was obtained from all patients.

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Received: 5 September 2015 Accepted: 19 October 2016
Published online: 02 November 2016

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