A dose exploration, phase I/II study of administration of continuous erythropoietin receptor activator once every 3 weeks in anemic patients with multiple myeloma receiving chemotherapy

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ABSTRACT

Background and Objectives

Continuous erythropoietin receptor activator (C.E.R.A.) is an innovative agent with unique erythropoietin receptor activity and a prolonged half-life, which has the potential for administration at extended dosing intervals. The objectives of this dose-finding study were to evaluate the hemoglobin (Hb) dose-response, pharmacokinetics, and safety of repeated doses of C.E.R.A. given once every 3 weeks to anemic patients with multiple myeloma (MM) receiving chemotherapy.

Design and Methods

This was an exploratory two-stage, open-label, parallel-group, multicenter study. Patients received C.E.R.A. doses of 1.0, 2.0, 3.5, 4.2, 5.0, 6.5, or 8.0 µg/kg once every 3 weeks by subcutaneous injection initially for 6 weeks, followed by a 12-week optional extension period. The primary outcome measures were the average Hb level and its change from baseline over the initial 6-week period, based on values of the slope of the linear regression analysis and the area under the curve. Rates of Hb response (defined as an increase in Hb of ≥2 g/dL without transfusion) and blood transfusion were also evaluated.

Results

Sixty-four patients entered the study. Dose-related increases in Hb levels were observed during the initial 6-week treatment period for C.E.R.A. doses of 1.0-4.2 µg/kg, with a similar response observed at higher doses. At least 70% of patients receiving 2.0-8.0 µg/kg of C.E.R.A. had Hb responses during the 18-week study. The elimination half-life of C.E.R.A. was found to be long (6.3-9.7 days [151.2-232.8 hours]). All doses were generally well tolerated.

Interpretation and Conclusions

Based on its unique, long elimination half-life, C.E.R.A. has been demonstrated to be an effective and well-tolerated treatment of anemia given once every 3 weeks to patients with multiple myeloma receiving chemotherapy.

Key words: anemia, C.E.R.A., chemotherapy, erythropoietin, multiple myeloma.

Anemia affects more than two-thirds of patients with lymphoid malignancies.[1,2] Cytotoxic chemotherapy may exacerbate this anemia, leading to fatigue, weakness, and reduced quality of life (QoL).[3,4] In multiple myeloma, bone marrow infiltration of the tumor is common and concomitant renal failure is frequently associated with defective endogenous erythropoietin production.[5] Consequently, transfusions are common in patients with multiple myeloma.[6,7]

Recombinant erythropoietic-stimulating agents (ESA) can correct anemia associated with lymphoid malignancies, increasing hemoglobin (Hb) levels, reducing blood transfusions and improving QoL.[1,8-10] The currently used dosing regimens of ESA often involve frequent administration (e.g. three times weekly). A once-weekly administration schedule of epoetin β was shown to correct anemia in patients with lymphoproliferative malignancies.[9] However, further reduction in the frequency of administration is limited by the relatively short half-life of epoetin. A once-weekly schedule of darbepoetin α also proved effective, specifically in patients with lymphoid malignancies,[10] and darbepoetin α has been licensed recently for administration once every 3 weeks. Extended dosing intervals of ESA may provide benefits to patients and physicians. Since many oncology treatments are administered in 3-weekly cycles, once-per-cycle administration may provide optimal convenience and compliance. The development of a new treatment for anemia with improved early and sustained Hb response over current treatments, while allowing co-ordination with chemotherapy administration, would represent an important advance in the management of anemia. Continuous erythropoietin receptor activator (C.E.R.A.) is an innovative agent with unique receptor activity and a prolonged half-life. It is a chemically synthesized continuous erythropoietin receptor activator, differing from erythropoietin through the integration of amide bonds between amino groups and methoxy polyethylene glycolsuccinimidyl butanoic acid.[11,12] C.E.R.A. is currently in development to provide correction of anemia and stable control of Hb levels at extended administration intervals in patients with cancer. Previous studies in healthy volunteers demonstrated that C.E.R.A. had lower systemic clearance and an increased elimination half-life compared with ESA and superior potency *in vivo* with respect to the magnitude and duration of response.[13,14] Further studies in healthy volunteer demonstrated rapid, dose-dependent increases in reticulocytes following either intravenous (i.v.) or subcutaneous (s.c.) administration.[15]

This phase I/II dose-finding study was designed to examine the Hb dose-response, pharmacokinetics, and safety of multiple doses of C.E.R.A. given once every 3 weeks to anemic patients with multiple myeloma receiving chemotherapy.

Design and Methods

Patients

Patients eligible for inclusion were adults (aged ≥18 years) with a cytologically or histologically confirmed diagnosis of multiple myeloma, with Hb level ≤11 g/dL at screening and who were scheduled to receive systemic anticancer therapy for at least the first 6 weeks of C.E.R.A. administration. Limits were set for levels of serum erythropoietin at screening: ≤70 U/L if Hb was >10 to ≤11 g/dL; ≤100 U/L if Hb was >9 to ≤10 g/dL; ≤180 U/L if Hb was >8 to ≤9 g/dL; and ≤300 U/L if Hb was ≤8 g/dL. Other inclusion criteria were World Health Organization (WHO) performance status grade 0-2, transferrin saturation >20% at screening, and a life expectancy >6 months.

Patients were excluded if they: had received a red blood cell transfusion within 2 months of the first planned dose of study medication or an ESA within 3 months; had known resistance to ESA therapy; had resistant hypertension; had acute or chronic bleeding requiring treatment within 3 months of the study; had grade 3/4 thrombocytopenia (platelet count <50×10^9/L) or thrombocytosis (platelet count >450×10^9/L); had creatinine >2.5 mg/dL, folic acid or vitamin B$_{12}$ deficiency, hemolysis. or epilepsy (uncontrolled or newly diagnosed within the last 6 months); were pregnant or lactating.

Study design

This was an exploratory 18-week, two-stage, open-label, parallel-group, multicenter, dose-finding study. The design and conduct of the study complied with the principles of good clinical practice, in accordance with the Declaration of Helsinki. The study was approved by local ethics committees at each center, and informed written consent was obtained from all patients before enrollment.

Following a screening period of up to 4 weeks, patients were randomized to receive C.E.R.A. 2.0 μg/kg, 3.5 μg/kg, or 5.0 μg/kg (stage I of the study) by s.c. injection once every 3 weeks for 6 weeks. Following a review of the data, two additional groups of patients were enrolled in a sequential manner into stage II of the study: the first group received s.c. C.E.R.A. 6.5 μg/kg and the second received 1.0 μg/kg once every 3 weeks for 6 weeks. After review of the data for these two groups, two further groups of patients were enrolled: the first receiving C.E.R.A. 8.0 μg/kg once every 3 weeks and the second receiving 4.2 μg/kg once every 3 weeks.

During the initial 6-week treatment period, the study medication was administered on day 1 and day 22. Patients attended the clinic weekly, when Hb, hematocrit and reticulocyte levels, electrocardiogram (ECG), safety laboratory and iron parameters, and blood pres-

sure measurements were taken. Blood transfusions were permitted throughout the study. Every reasonable effort was made to avoid transfusions in patients with Hb levels >8.5 g/dL, particularly during the initial 6-week treatment period. The need for blood transfusions was determined at the discretion of the investigator, based on the patient's symptoms and local practice. All transfusions were recorded and specified by type and volume. Following the initial 6-week treatment period, with the agreement of the patient, investigator and sponsor, patients continued to receive the study medication once every 3 weeks for up to 12 additional weeks in an optional extension period. Clinic visits were scheduled every 3 weeks during this period, when Hb, hematocrit and reticulocyte levels, ECG, safety laboratory and iron parameters, and blood pressure were measured. Adverse events were monitored throughout the study and, with regard to serious adverse events, up to 30 days after the final administration of the drug. Safety evaluations also included clinical laboratory tests, ECG, vital signs, and measurement of anti-CERA antibodies. Adverse events were graded according to the National Cancer Institute/National Institutes of Health (NCI/NIH) Common Toxicity Criteria. Tolerability was evaluated based on the number of patients prematurely withdrawn from the study for safety reasons.

Dose adjustments

Limited C.E.R.A. dose reductions were allowed during the initial and extension periods for the following safety reasons: first, if Hb levels increased by >2.5 g/dL in any 6-week period, the next C.E.R.A. dose was decreased by 50% without interruption of dosing; second, if Hb levels exceeded 14 g/dL at any time, treatment was stopped until a Hb level of <13 g/dL was reached and resumed at 50% of the previous dose; third, if a grade 2 or greater acute toxicity occurred which was considered at least possibly related to the study medication (based on experience with ESA in patients with cancer), the treatment could be interrupted if considered necessary by the investigator. Following resolution of the toxicity, the study medication could be resumed at the previous dose. However, if toxicity recurred, the patient was to be withdrawn from the study and followed up until recovery.

Dose increases of C.E.R.A. were only permitted during the extension period and only if Hb levels had not increased by at least 1 g/dL from the baseline value. The dose was only allowed to be increased up to the highest previously tested dose. Thus, at week 7, patients assigned to the C.E.R.A. 2.0 and 3.5 µg/kg groups and 1.0 µg/kg group could have their dose increased to a maximum of 5.0 µg/kg once every 3 weeks. Patients assigned to the 4.2 µg/kg group could have their dose increased to a maximum of 6.5 µg/kg.

Efficacy end-points

The primary efficacy end-point was the average increase in Hb level from baseline up to the end of initial treatment based on the area under the curve (AUC) values and the slope of the linear regression line. The end of initial treatment was defined as the time when the assessment period was complete, a dose change was introduced, or a blood transfusion was given, whichever occurred first. Secondary efficacy end-points included rates of Hb response and blood transfusions and average hematocrit levels and reticulocyte counts during the study. A Hb response was defined as an increase in Hb level of ≥2 g/dL from baseline during the initial 6-week treatment period without blood transfusion.

Pharmacokinetic evaluations

Blood samples were taken for analysis of pharmacokinetic parameters before the first administration of the study medication on day 1 and on days 8, 15, 22 (before the second administration of the study drug), 23, 27, 29, and 32 and before each C.E.R.A. administration during the extension period. The pharmacokinetic parameters of maximum serum concentration (C_{max}), time to C_{max} (T_{max}), elimination half-life ($t_{1/2}$), and $AUC_{22\text{-}43\ days}$ were calculated for each patient. $t_{1/2}$ was estimated from $\ln(2)/k$, where the rate constant of elimination (k) was determined by linear regression on the logarithm of the serum concentration-time data in the post-distribution phase. $AUC_{22\text{-}43\ days}$ was estimated by the linear trapezoidal rule.

Statistical analyses

This was an exploratory study and no formal sample size calculation was performed. A total of eight patients were planned to be included in each dose group. All efficacy end-points were analyzed based on the intention-to-treat (ITT) population comprising all patients who were randomized (stage I) or enrolled (stage II) and received at least one dose of study medication.

The primary analysis focused on the initial 6 weeks of treatment, with additional analyses for the entire study period (including the extension period). The primary efficacy end-point, change in Hb, was calculated for each patient using a separate linear regression over time with the Hb level as the dependent variable; the mean of all measurements on or before baseline was used as the day 1 value. The regression slopes, which are estimates of the Hb change per day, were multiplied by 42 for standardization and to give an estimate of Hb increases after 6 weeks of treatment. Slopes were summarized using means, standard deviations (SD), medians, and minimum and maximum values. Average Hb changes from baseline during the initial 6-week period were also estimated by an AUC approach. The area under the Hb curve until end of initial treatment was calculated for each patient using the trapezoidal rule. The secondary end-point of change from baseline in
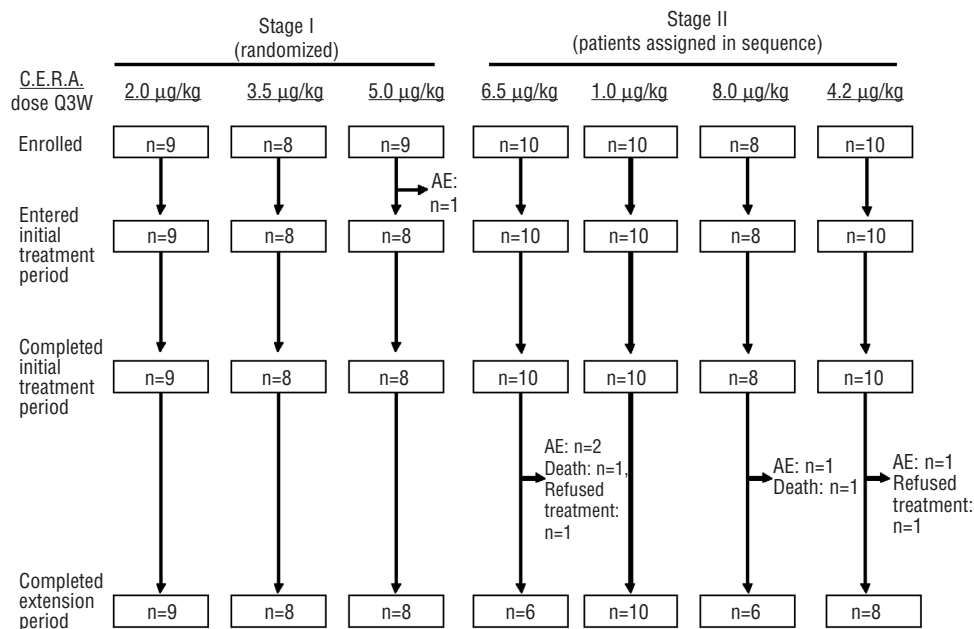
C.E.R.A. dose Q3W	Stage I (randomized)			Stage II (patients assigned in sequence)			
	2.0 μg/kg	3.5 μg/kg	5.0 μg/kg	6.5 μg/kg	1.0 μg/kg	8.0 μg/kg	4.2 μg/kg
Enrolled	n=9	n=8	n=9	n=10	n=10	n=8	n=10
			→ AE: n=1				
Entered initial treatment period	n=9	n=8	n=8	n=10	n=10	n=8	n=10
Completed initial treatment period	n=9	n=8	n=8	n=10	n=10	n=8	n=10
				→ AE: n=2 Death: n=1, Refused treatment: n=1		→ AE: n=1 Death: n=1	→ AE: n=1 Refused treatment: n=1
Completed extension period	n=9	n=8	n=8	n=6	n=10	n=6	n=8

Figure 1. Disposition of patients, including reasons for withdrawal.

AE: adverse event; CERA: continuous erythropoietin receptor activator; Q3W: once every 3 weeks.

hematocrit was analyzed using identical regression and AUC methods as described above. For reticulocyte counts, only the AUC analysis was performed. Descriptive statistics were used to analyze the additional efficacy end-points. Pharmacokinetic end-points were analyzed for all patients who provided evaluable samples. Estimates of pharmacokinetic parameters were performed according to standard non-compartmental methods, using WinNonlin version 4.1 (Pharsight, Mountain View, CA, USA) and based on actual sampling times. Pharmacokinetic parameters were calculated for each patient from the concentration-time data obtained after the second administration of the drug, from day 22 to day 43. All safety data were summarized using descriptive statistics.

Results

Disposition of patients

Sixty-four patients were enrolled at five centers in Poland and the Czech Republic, 26 patients in stage I and 38 in stage II of the study. Similar numbers of patients were assigned to each dose level of CERA (Figure 1). One patient in the 5.0 μg/kg group did not receive the study medication because of an adverse event (renal failure) occurring in the screening period, and was excluded from all analysis populations. The remaining 63 patients all completed the initial 6-week treatment period, entered the extension period, and were included in the ITT and safety analyses (Figure 1).

Fifty-five patients (87%) completed the extension period, and eight patients were withdrawn prematurely (Figure 1). The second dose of CERA in the initial treatment period was withheld from one patient in the 4.2 μg/kg group because of adverse events (fatigue and fungal pneumonia). This patient entered the extension period but subsequently died (for reasons described by the investigator as unrelated to the study medication) on day 44. Of the remaining seven patients, three were withdrawn because of adverse events that were described by the investigator as unrelated to the study medication, two patients died for reasons described as unrelated to the study medication, and two patients refused further treatment (Figure 1).

Baseline characteristics

Baseline characteristics and demographics were similar in all groups (Table 1). Mean Hb levels ranged from 9.8-10.4 g/dL and mean hematocrit from 30.5-32.2% across the dose groups. In accordance with the inclusion criteria, median serum erythropoietin levels were <70 IU/L and the median ratio of observed to predicted $\log_{10}$ serum erythropoietin levels (O/P ratios) were <1 in all treatment groups (Table 1). Most patients had stage 2A or 3A disease based on the Durie and Salmon classification[16] (49% and 35% of patients, respectively) and, in most patients, the serum monoclonal (M) protein was of the IgG type (36 of 63 patients; 57%). Most patients had a WHO performance status of 1 (40 of 63 patients; 63.5%). The most frequently used anticancer therapies were combination regimens with or without anthracyclines (44 of 63 patients; 70%).

Efficacy

Although the number of patients assigned to each dose group of C.E.R.A. was small and there tended to be some variability in the results, the median change in Hb

levels during the initial 6-week period showed dose-related increases in response to C.E.R.A. once every 3 weeks over the dose range 1.0-4.2 µg/kg (Figure 2). The median increase in Hb level was greatest in the 4.2 µg/kg group, being 2.21 g/dL, with similar increases observed for the 5.0, 6.5, and 8.0 µg/kg groups. In contrast, the median increase in Hb level was only 0.03 g/dL in the 1.0 µg/kg group, suggesting a suboptimal response to this dose of C.E.R.A. (Figure 2). The AUC analysis provided a similar trend. After the initial treatment period, Hb levels were maintained or continued to increase and were then maintained for the remainder of the study (Figure 3).

During the initial treatment period, median hematocrit levels remained unchanged in the 1 µg/kg group, but were increased from baseline in the other dose groups: to 33.9% in the 2.0 µg/kg group, to 36-37% in the 3.5-5.0 µg/kg groups, to 43.6% in the 6.5 µg/kg

group, and to 38.9% in the 8.0 µg/kg group. AUC analysis of reticulocyte counts showed a progressive increase in the median baseline adjusted AUC over the initial treatment period across the entire range of C.E.R.A. doses examined. The performance status of most patients was maintained or improved over the duration of the study (*data not shown*).

Approximately 60% of patients receiving C.E.R.A. doses of 3.5-8.0 µg/kg had a Hb response during the initial 6-week treatment period, defined as an increase of Hb ≥2.0 g/dL relative to baseline levels without transfusion (Figure 4). During the complete 18-week study period, only 20% of patients in the 1.0 µg/kg dose group demonstrated a Hb response, suggesting that this dose was sub-optimal in anemic patients with multiple myeloma. In comparison, ≥70% of patients assigned to the 2.0 µg/kg or higher dose groups had a Hb response. A Hb response occurred in 78% of patients in the 2.0

**Table 1.** Patients' characteristics at baseline by treatment group: safety population.

	C.E.R.A. dose group, µg/kg once every 3 weeks						
	1.0	2.0	3.5	4.2	5.0	6.5	8.0
Numbers	10	9	8	10	8	10	8
Sex, n (%)							
male	3 (30)	2 (22)	3 (37)	6 (60)	3 (37)	3 (30)	1 (13)
female	7 (70)	7 (78)	5 (63)	4 (40)	5 (63)	7 (70)	7 (87)
Median age, years (range)	62.5 (41-76)	71.0 (45-84)	64.5 (45-83)	64.5 (52-75)	63.5 (44-81)	70.0 (57-77)	67.5 (53-81)
Median weight, kg (range)	67.5 (55-80)	69.0 (36-89)	68.0 (50-83)	70.0 (54-90)	74.0 (45-97)	63.5 (46-80)	59.25 (55-76)
Median time from initial diagnosis, days (range)	177.5 (34-5382)	225.0 (24-1262)	183.5 (36-2176)	341.5 (15-4166)	195.5 (17-1708)	232.5 (45-2420)	159.5 (13-4136)
Median Hb, g/dL (range)	10.0 (8.7-10.8)	9.7 (6.9-11.5)	10.2 (9.3-10.7)	10.2 (8.1-11.3)	10.4 (9.6-11.1)	9.8 (8.7-11.0)	10.4 (7.8-11.1)
Median hematocrit, % (range)	31.9 (27.6-35.8)	31.2 (22.6-36.1)	31.4 (28.0-32.6)	31.9 (25.7-38.4)	31.6 (29.0-36.2)	31.5 (29.1-35.5)	33.7 (25.5-35.9)
Median reticulocyte count, 10^3/µL (range)	49.5 (31.5-75.5)	37.5 (18.5-88.0)	71.3 (20.0-104.0)	41.8 (17.5-111.0)	40.5 (19.0-78.5)	53.8 (25.0-83.5)	47.8 (25.0-68.0)
Median serum creatinine, µmol/L (range)	72 (59-114)	97 (59-152)	94 (76-210)	89 (74-220)	92 (80-187)	93 (81-184)	82 (57-97)
Median serum iron, µmol/L (range)	15.6 (10.9-22.7)	12.9 (4.5-24.2)	15.7 (11.8-33.8)	12.0 (5.9-20.9)	14.4 (7.9-19.3)	13.0 (6.1-19.7)	10.7 (8.8-16.3)
Median ferritin, µg/L (range)	394 (111-3300)	553 (31-1487)	400 (101-1293)	180 (22-1390)	245 (97-801)	368 (143-1265)	644 (60-1331)
Median transferrin, mg/dL (range)	1.8 (1.4-2.3)	2.2 (1.1-3.1)	1.9 (1.4-2.4)	2.2 (1.3-3.4)	2.2 (1.3-2.6)	1.7 (1.2-2.6)	1.7 (1.6-2.5)
Median TSAT, % (range)	33 (21-59)	23 (12-42)	34 (20-77)	21 (12-38)	28 (13-45)	30 (15-37)	23 (16- 40)
Median serum EPO level, IU/L (range)	51.9 (17.5-161.0)	34.4 (12.3-190.0)	33.0 (15.3-93.6)	38.8 (12.3-121.0)	31.7 (8.2-62.0)	31.8 (11.4-58.9)	42.2 (22.6-70.8)
O/P ratio, median (range)	0.976 (0.705-1.335)	0.811 (0.500-1.106)	0.789 (0.725-0.994)	0.864 (0.668-1.292)	0.824 (0.461-1.004)	0.852 (0.571-1.137)	0.925 (0.669-1.107)

CERA: continuous erythropoietin receptor activator; EPO: erythropoietin; Hb: hemoglobin; O/P ratio: the ratio of observed to predicted $\log_{10}$ serum erythropoietin (EPO) levels; TSAT: transferrin saturation.
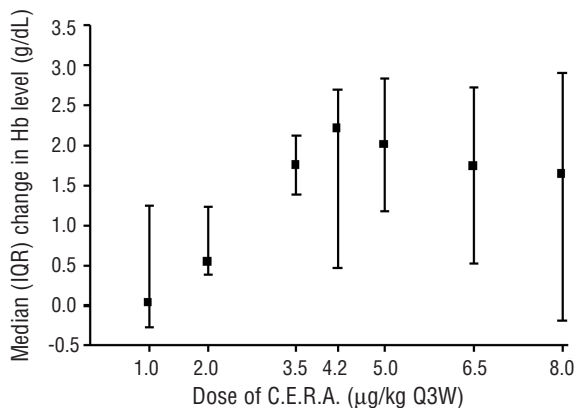
C.E.R.A.: continuous erythropoietin receptor activator; Hb: hemoglobin;
IQR: interquartile range; Q3W: once every 3 weeks.

Figure 2. Change in hemoglobin from baseline to end of initial treatment based on regression slope analysis for the 6-week initial treatment period: intention-to-treat population.
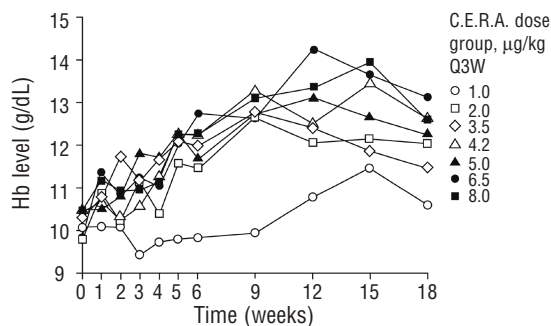

The Hb level shown at time 0 represents the baseline value (please see statistical section for explanation of how the baseline value was determined).
C.E.R.A.: continuous erythropoietin receptor activator; Hb: hemoglobin;
Q3W: once every 3 weeks.

Figure 3. Median hemoglobin levels over the entire study period: intention-to-treat population.

μg/kg group, in 100% in the 3.5 μg/kg group, in 70% in the 4.2 μg/kg group, in 100% in the 5.0 μg/kg group, in 90% in the 6.5 μg/kg group and in 75% in the 8.0 μg/kg group. The percentages of patients who never had a dose modification during the study were 10% in the 1.0 μg/kg group, 33% in the 2.0 μg/kg group, 50% in the 3.5 μg/kg group, 11% in the 4.2 μg/kg group, 50% in the 5.0 μg/kg group, 30% in the 6.5 μg/kg group, and 50% in the 8.0 μg/kg group. Modifications to the C.E.R.A. dose during the extension period generally consisted of reductions, particularly in the higher-dose groups. The exception was the 1.0 μg/kg group, in which nine out of the ten patients had their C.E.R.A. dose increased.

Thirteen patients (21%) received blood transfusions during the study, seven during the initial 6-week treatment period and six during the extension period. In all but three patients (who had transfusions because of anemia-related symptoms within the first 5 weeks of the study at Hb levels of 8.6, 8.8 or 8.9 g/dL), the Hb
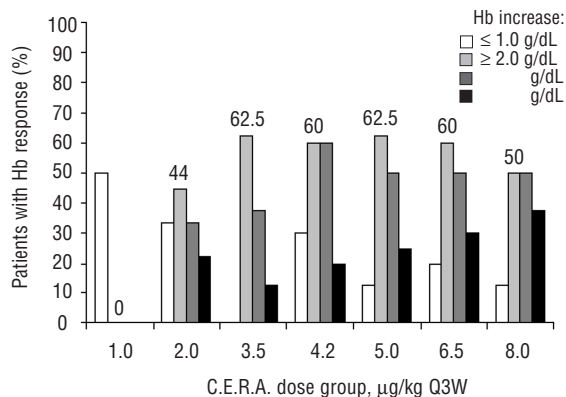
Numbers above the bars represent the percentages of patients with a hemoglobin (Hb) response (defined as a Hb increase ≥2.0 g/dL relative to baseline without transfusion during the initial 6-week treatment period). No patients receiving 1.0 μg/kg C.E.R.A. achieved a Hb response. C.E.R.A.: continuous erythropoietin receptor activator; Hb: hemoglobin; Q3W: once every 3 weeks.

Figure 4. Proportion of hemoglobin responders during the *initial 6-week period* study: intention-to-treat population.

level at transfusion was ≤8.5 g/dL. There was no clear relationship between the dose of C.E.R.A. and the number and/or volume of blood transfusions given. Sixty percent of patients receiving the 1.0 μg/kg dose, 78% receiving 2.0 μg/kg, 87.5% receiving 3.5 μg/kg, 80% receiving 4.2 μg/kg, 100% receiving 5.0 μg/kg, 80% receiving 6.5 μg/kg, and 75% receiving 8.0 μg/kg remained transfusion-free.

Pharmacokinetics

In total, 54 of the 63 patients (86%) were evaluable for the pharmacokinetic analysis. Mean C.E.R.A. concentration-time profiles over the entire study period are shown in Figure 5. Mean serum concentrations increased with doses up to 4.2 μg/kg. At higher doses, only small further increases were seen; systemic exposure seemed to plateau, especially for C_{max}.

Pharmacokinetic parameters obtained following the second administration of C.E.R.A. (on day 22) are summarized in Table 2. Overall, the median T_{max} ranged from 4.5 to 7.0 days, and median $t_{1/2}$ from 6.3 to 9.7 days (151.2-232.8 hours). These values did not change markedly with dose of C.E.R.A. administered. C_{max} and $AUC_{22-43\ days}$ increased with C.E.R.A. doses up to 4.2 μg/kg, with no or only small increases at higher doses.

Tolerability and safety

C.E.R.A. was generally well tolerated. Although 78% of patients had adverse events, most were mild to moderate in intensity and were not considered by the investigator to be related to C.E.R.A. therapy, but rather to the underlying disease and its treatment. Also, there did not appear to be any dose-related trends in the incidence and type of adverse events reported. The most frequently reported adverse events across all treatment groups were hypertension, diarrhea and leukopenia.

Table 2. Pharmacokinetic parameters following the second administration of C.E.R.A. (day 22).

	C.E.R.A. dose group, µg/kg once every 3 weeks						
	1.0	2.0	3.5	4.2	5.0	6.5	8.0
n	10	6*	8	7	8	10	5
Mean (±SD) C_{max} (ng/mL)	4.08±3.85	6.40±2.15	18.4±6.85	26.1±10.4	23.4±6.5	22.5±11.6	25.7±21.7
Median T_{max} (days)	6.85	6.92	4.47	6.85	5.00	6.96	6.87
Mean (±SD) $AUC_{22-43 days}$ (day · ng/mL)	57.6±52.4	93.5±29.1	245±85.4	344±112	286±76.0	315±133	380±326
Median $t_{1/2}$ (days)	6.30	9.71	9.51	7.04	8.51	6.72	8.01

*One patient had values below the limit of quantification in all samples. $AUC_{22-43 days}$, area under the concentration time curve between days 22 and 43; C.E.R.A.: continuous erythropoietin receptor activator; C_{max}: maximum serum concentration; SD: standard deviation; T_{max}: time to C_{max}; $t_{1/2}$: elimination half-life; Q3W: once every 3 weeks.

Generally comparable proportions of patients in each treatment group were reported to have suffered each individual event.

Seven adverse events in six patients were considered by the investigator to be related to treatment with C.E.R.A.: in one patient each in the 1.0, 2.0, 3.5, 4.2, 5.0, and 6.5 µg/kg groups (but none in the 8.0 µg/kg group). The adverse events were hypertension of mild to moderate intensity in five patients, which was controlled adequately with antihypertensive medication, pyrexia of mild intensity in one patient, and allergic dermatitis of moderate intensity at the injection site in one patient. The dose of C.E.R.A. was withheld on day 106 in the patient with allergic dermatitis and this event resolved with triamcinolone treatment. Six patients died during the study or during the 30-day follow-up. None of these deaths were considered by the investigator to be related to the C.E.R.A. treatment.

There were no clinically significant changes from baseline in laboratory values assessed during the study and no trend was reported for increasing blood pressure with treatment. Seated diastolic and systolic blood pressures were relatively unchanged throughout the study in all treatment groups, with median changes generally within 5 mmHg. No anti-C.E.R.A. antibodies were detected.

Discussion

Anemia is a common complication of multiple myeloma, being present in approximately two-thirds of patients with this disease at the time of diagnosis.[17] Treatment options include blood transfusions and ESA. Transfusions lead to only transient responses and are associated with several risks and supply issues. In contrast, ESA lead to sustained increases in Hb levels, reduced need for transfusions, and improved QoL in anemic patients with cancer.[18] The use of ESA has been recommended in patients with multiple myeloma.[17] Most ESA regimens involve once-weekly or more frequent dosing. New treatments allowing for less frequent administration and co-ordination of dosing with chemotherapy regimens, together with improved early
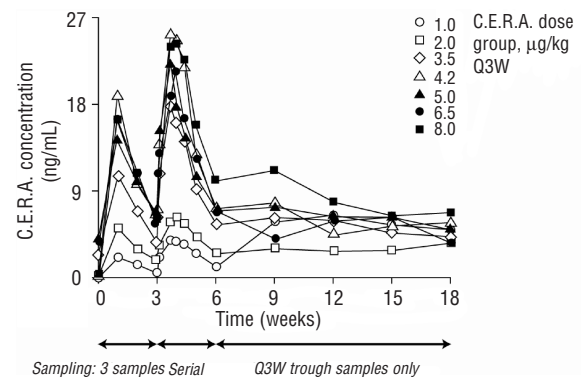
Time 0 points represent the blood samples obtained on the first day of study before the administration of C.E.R.A. C.E.R.A.: continuous erythropoietin receptor activator: Q3W: once every 3 weeks.

Figure 5. Mean serum CERA concentration-time profiles by dose group over the entire study period:

and sustained Hb response, would be an advantage in the treatment of anemia in the setting of oncology. C.E.R.A. is the first continuous erythropoietin receptor activator being developed for the control of anemia in patients with cancer. Studies in healthy volunteers demonstrated that C.E.R.A. had a prolonged serum half-life, with the potential for administration at extended intervals when compared with the ESA.[13,14] An additional benefit of C.E.R.A. is that it has an approximately 100-fold lower binding affinity for the erythropoietin receptor, driven mainly by a slower association rate,[19] suggesting that it has the potential for a continuous effect on erythropoiesis. This would be beneficial in patients with cancer who are receiving several cycles of chemotherapy.

This dose-exploration study examined the Hb dose-response, pharmacokinetics, and safety of repeated doses of C.E.R.A. given once every 3 weeks in anemic patients with multiple myeloma receiving chemotherapy. Most patients had stage 2A or 3A multiple myeloma, with the IgG type of serum M protein, features consistent with a population of patients with multiple

myeloma. Average Hb change from baseline to the end of initial treatment indicated a dose-related erythropoietic response to C.E.R.A. at doses of 1.0-4.2 µg/kg. The median increase in Hb level was 2.21 g/dL in the group receiving 4.2 µg/kg once every 3 weeks during the initial 6-week treatment period, with higher doses resulting in a similar Hb increase to that in the 4.2 µg/kg group. Moreover, approximately 60% of patients receiving C.E.R.A. 3.5-8.0 µg/kg once every 3 weeks experienced a Hb response (defined as an increase of ≥2.0 g/dL) during the initial treatment period, indicating a rapid onset of effect. This level of response was improved or maintained during the remainder of the study, as a Hb response was demonstrated in ≥70% of patients receiving doses of ≥2.0 µg/kg during the extension period. This study indicated that a dose 1.0 µg/kg once every 3 weeks dose was suboptimal in most anemic patients with multiple myeloma. A comparison of efficacy between dose groups is difficult given the small numbers of patients in each group and the fact that the patients were not randomized into stage II. Nevertheless, doses of 3.5-8.0 µg/kg once every 3 weeks resulted in clinically relevant efficacy, suggesting the suitability of evaluating this dose range in further studies of C.E.R.A. in anemic patients with cancer. Other studies of ESA in lymphoid malignancies allowed dose-doubling if a predefined Hb increase was not reported after ~4 weeks of treatment.[8-10] As the present study was a dose-exploration study, no dose increases were allowed during the first 6 weeks, while only limited dose increases were allowed in the extension period. Modifications to the C.E.R.A. dose during the extension period generally consisted of reductions, particularly in the higher dose groups. The exception was the 1.0 µg/kg group, in which nine of ten patients had their C.E.R.A. dose increased. Very high Hb response rates to C.E.R.A. were observed in the current study (in the range of 70-100% during the entire study period for doses ≥2 µg/kg once every 3 weeks). This level of response to C.E.R.A. compares favorably with the results of studies with ESA in patients with multiple myeloma or other lymphoproliferative malignancies. A double-blind, placebo-controlled study of epoetin α 150-300 IU/kg three times weekly produced a Hb response and/or avoidance of transfusion requirement in 75% of multiple myeloma patients, together with reduced fatigue and improved QoL.[6] Randomized studies evaluating epoetin β in patients with lymphoproliferative malignancies (multiple myeloma, non-Hodgkin's lymphoma and chronic lymphocytic leukemia) showed Hb responses in 67-75% of patients with three times weekly dosing[8,9] and in 72% with once-weekly dosing.[9] A double-blind, placebo-controlled study with darbepoetin α given once weekly to patients with lymphoproliferative malignancies resulted in a Hb response in 60% of patients.[10] However, the extended administration interval of once every 3 weeks used in the present study

has not been tested with any ESA specifically in patients with multiple myeloma. The pharmacokinetic parameters of C.E.R.A. given once every 3 weeks demonstrated a long T_{max} of 4.5-7.0 days and a long $t_{1/2}$ of 6.3-9.7 days (151.2-232.8 hours), both values being relatively independent of the dose of C.E.R.A. There appeared to be a plateau effect in serum concentration-time profiles, C_{max} and $AUC_{22-43\ days}$ at doses >4.2 µg/kg. This plateau effect may be a result of the small numbers of patients in each group and the small increments in dose between groups. The values for $t_{1/2}$ were considerably longer than those reported for epoetin β in healthy volunteers (approximately 24 hours)[20] or darbepoetin α in patients with cancer (approximately 61-88 hours, depending on the timing of the chemotherapy).[21] These data provide a scientific rationale for using C.E.R.A. at extended administration intervals. C.E.R.A. was generally well tolerated in the study. Most adverse events were attributed to the underlying disease or chemotherapy rather than to the study drug. There were no dose-related trends in adverse events, although it is difficult to compare the incidence of individual adverse events between the groups because of the small numbers of patients and also because patients were not randomized into the second stage of the study. This was the first study to evaluate C.E.R.A. in patients with cancer; therefore, the adverse event profile, including adverse events possibly related to therapy, is not currently known in these patients. Based on studies of anemia correction using ESA in the setting of oncology, adverse events considered by the investigator to be possibly related to the study medication included five cases of hypertension, which was controlled adequately with antihypertensive medication, and single cases of pyrexia and allergic dermatitis at the injection site. These adverse events occurred at a similar frequency to those reported in studies of ESA in patients with multiple myeloma or other lymphoid malignancies.[6,8] There were no clinically significant changes from baseline in vital signs or body weight. In addition, no clinically significant changes or worsening of pre-existing abnormalities were observed in ECG during the study.

As for other phase I/II studies, limitations of the current study included its small size and the lack of a control group. Nevertheless, the promising results reported here suggest that large, randomized and controlled studies are warranted to investigate further the clinical profile of C.E.R.A. in other malignancies. Results from this study indicate that a dose range of 3.5-8.0 µg/kg may be effective in the setting of oncology, although this needs to be confirmed in bigger trials including other types of cancer. The design of future studies should also allow for increasing the C.E.R.A. dose in the event of an inadequate Hb response.

C.E.R.A., administered once every 3 weeks to anemic patients with multiple myeloma, was generally well tolerated and resulted in a dose-dependent and sustained

increase in Hb levels. Doses of C.E.R.A. of 3.5-8.0 µg/kg appeared to result in clinically relevant efficacy. This supports the use of such doses in future studies in other types of cancer.

This is the first study to have evaluated C.E.R.A. administered once every 3 weeks to patients with cancer. The unique mode of action and pharmacokinetic profile of C.E.R.A. demonstrated in this population of cancer patients support the tested prolonged interval between injections that may enable administration to be synchronized with chemotherapy and improve convenience and flexibility of treatment in patients with multiple myeloma. The results of other studies using C.E.R.A. in the management of anemia in patients with cancer are awaited.

Authors' Contributions

AD: conception and design of the study, acquisition of data, analysis and interpretation of data, determining manuscript content, revising manuscript critically for important intellectual content, final approval of the version to be published; JK, MR, AH, IS: conception and design of the study, acquisition of data, analysis and interpretation of data, revising manuscript critically for important intellectual content, final approval of the version to be published; JEE: analysis and interpretation of data, drafting the article, revising manuscript critically for important intellectual content, final approval of the version to be published.

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