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2004 Japanese Society for Dialysis Therapy Guidelines for Renal Anemia in Chronic Hemodialysis Patients*

Fumitake Gejyo,[1] Akira Saito,[2] Tadao Akizawa,[3] Takashi Akiba,[4] Tatsuya Sakai,[5] Masashi Suzuki,[6] Shinichi Nishi,[7] Yoshiharu Tsubakihara,[8] Hideki Hirakata,[9] and Masami Bessho[10]

[1]Graduate School of Medical and Dental Sciences, Division of Clinical Nephrology and Rheumatology, Niigata University, Niigata, [2]Department of Molecular Nephrology, Institute of Medical Science, Tokai University, Kanagawa, [3]Blood Purification Center, Wakayama Medical University Hospital, Wakayama, [4]Department of Blood Purification, Kidney Disease General Medical Center, Tokyo Women's Medical College, Tokyo, [5]Department of General Medicine & Clinical Epidemiology, Kyoto University School of Medicine, Kyoto, [6]Kidney Center, Shinraku-En Hospital, Niigata, [7]Blood Purification Center, Niigata University Medical and Dental Hospital, Niigata, [8]Department of Nephrology, Osaka General Medical Center, Osaka, [9]Kidney Care Unit, Kyushu University Hospital, Fukuoka, and [10]Department of Hematology, Saitama Medical School, Saitama, Japan

Abstract: The guideline committee of Japanese Society for Dialysis Therapy (JSDT), chaired by Professor F. Gejyo of Niigata University, now publishes an original Japanese guideline entitled 'Guidelines for Renal Anemia in Chronic Hemodialysis Patients'. It includes the re-evaluation of the usage of recombinant human erythropoietin (rHuEPO) with the medical and economical arguments regarding the prognosis and the quality of life of Japanese hemodialysis patients. This guideline consists of 7 sections. The first section comprises the general definition and the differential diagnosis of anemia. The hemoglobin (Hb) level of the Japanese population seemed to be low when compared with that of the European and American populations. The second section describes the target Hb level in hemodialysis patients. Multivariate analysis of the data that were collected from dialysis institutions throughout the country showed that an Hb level of 10–11 g/dL (Ht level 30–33%) at the first dialysis session in a week is the ideal range for chronic hemodialysis patients in terms of the 3–5 year survival rate. The supine position at blood sampling and the sampling timing at the first dialysis session in a week might affect the lower setting of target Hb hematocrit (Ht), compared to that of European and American guidelines. However, we particularly recommended that an Hb level of 11–12 g/dL (Ht level from 33 to 36%) at the first dialysis session in a week is desirable in relatively young patients. In the third section, the markers of iron deficiency are discussed. The Transferin saturation test (TSAT) and serum ferritin were emphasized as the standard markers. The routes of administration of rHuEPO and its dosages are written in the fourth section. The subcutaneous route was associated with the occurrence of secondary red cell aplasia due to anti-rHuEPO antibodies; however, secondary red cell aplasia was seldom observed in the venous injection. From this fact we recommend venous injection for chronic hemodialysis patients. We advocate an initial dosage of 1500 U three times per week. The fifth section deals with the factors refractory to treatment with rHuEPO. If the patient shows an inadequate response to the usage of 9000 U per week, this condition defines the inadequate response to rHuEPO in Japan. Blood transfusion must be avoided where possible. The reasons for this and the adverse effects are interpreted in section six. In the final section, the adverse effects of rHuEPO are listed. Among them, hypertension, thrombotic events and secondary red cell aplasia were emphasized as the major complications. **Key Words:** Chronic hemodialysis, Guidelines, Hemoglobin, Recombinant human erythropoietin, Red cell aplasia, Renal anemia, Quality of life.

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Address correspondence and reprint requests to Dr Shinichi Nishi, Blood Purification Center, Niigata University Medical and Dental Hospital, 1–754 Asahimachi-dori, Niigata City 951–8520 Japan. Email: snishi@med.niigata-u.ac.jp

Renal anemia is related to deterioration of renal hypofunction; in particular, this disorder has been considered a serious complication in patients undergoing chronic hemodialysis (HD). Renal failure-related anemia is characterized by a normocytic and

normochromic state, selective hypoplasia of erythroblasts in the bone marrow, and hematopoietic hypofunction. A lack of production of erythropoietin (EPO) by the kidney tissue is mainly involved in the etiology. Recently, the clinical application of treatment with recombinant human erythropoietin (rHuEPO) has markedly changed anemia treatment in patients with renal failure. In Japan, 15 years have passed since treatment with rHuEPO for renal anemia was introduced, and currently, more than 80% of patients undergoing dialysis in Japan are treated with rHuEPO. According to the data collected by the Japanese Society for Dialysis Therapy (JSDT), the mean hematocrit (Ht) value in the patients undergoing dialysis in Japan in 1988 was 24.9%; however, the Ht value has increased year by year since an EPO preparation became commercially available in 1990, reaching 30.6% at the end of 2001. Erythropoietin preparations have markedly improved the prognosis and quality of life (QOL) for patients undergoing dialysis.

Recently, the views toward renal anemia treatment have markedly changed, and in Europe and the United States, the Guidelines for the Treatment of Renal Anemia were published, and have been routinely used (NKF-K/DOQI Guidelines (1997, 2001) in the United States, EDTA/ERA Guidelines (1999, 2000) in Europe)(3,4). However, in Japan, no guidelines for renal anemia treatment have been established. In addition, recently, new issues on rHuEPO therapy in Japan have been indicated from several perspectives. The first issue is the review of the target hemoglobin (Hb) hematocrit (Ht) values for improving anemia. Fifteen years have passed since a rHuEPO preparation became commercially available; however, at that time, it was published that 'the target value of Hb for improving anemia is approximately 10 g/dL (Ht: 30%)' in the dosage column of the Insurance Price List, and this value has been employed without revision. Therefore, therapeutic strategies involving many issues, such as the clinical significance of improving anemia to a value better than this value, appropriate administration routes/administration of iron supplements, and the management of non-responders to rHuEPO preparations and patients with pure red cell aplasia (PRCA), should be established. Based on the above background, it may be significant to prepare guidelines for the treatment of renal anemia matched to the status of dialysis treatment in Japan.

The JSDT established 'a working group for preparing the treatment guidelines on renal anemia in Japan' (Erythropoietin Working Group) consisting of 10 committee members specialized in this field. At a meeting held by this committee, a consensus was obtained that anemia is expressed using the Hb value and that it is recommended that the Ht value should be concurrently written. We tried to prepare our guidelines based on evidence; in particular, we collected data in Japan. However, there was no high-quality evidence in Japan. The statistical survey conducted by the JSDT is extremely accurate, but is not a prospective clinical study. Therefore, we added new analytical work to utilize the data as evidence in Japan. In addition, in the process of analyzing the evidence reported in Europe and the United States, the problems related to the difference in dialysis practice between Japan and Europe/United States were clinically reviewed at meetings held by this committee. We tried to prepare the guidelines in accordance with the status in Japan based on high-grade evidence with reference to the major studies published before 2003. Expressions for recommendation depended on the status in Japan and the extent of clinical indications on the basis of a consensus in this committee. In addition, to reflect opinions from the JSDT members, a preliminary report was presented at the 47th meeting held by the JSDT in Tokyo in July 2002, and the final report (draft) at the 48th meeting held by the JSDT in Osaka in June 2003. A consensus conference titled 'For preparing the guidelines for the treatment of renal anemia in Japan' was held. Valuable opinions from many members were adopted. Thus, a long period of time was required.

Our guidelines (revision in 2004) reflect the results of a review conducted by the JSDT members over the past 3 years. We publish 'the Guidelines for the Treatment of Renal Anemia in Patients Undergoing Chronic Hemodialysis'; however, we reviewed only patients undergoing chronic HD, and our guidelines do not involve anemia treatment in the preservative phase prior to dialysis or in patients undergoing continuous ambulatory peritoneal dialysis (CAPD)/transplantation. Our guidelines were arranged considering average patients undergoing chronic HD, and do not apply to all patients.

It would be our pleasure if our guidelines contributed to improving anemia treatment in patients undergoing dialysis in Japan. In the future, the guidelines should be revised if necessary based on new evidence in reference to comments from JSDT members and persons concerned.

CHAPTER I

Criteria for anemia and diagnosis of anemia

1. The physiological Hb value in healthy adults depends on age, gender, and race. Therefore, the

TABLE 1. *Mean hemoglobin levels in Japanese males and females and the criteria for anemia*

	(Japan Complete Book on Hematology, new edition) 20–59 years	(Chronological scientific) 60–69 years	70–79 years
male g/dL (mean ± SD)	14.8 ± 1.2	13.8 ± 0.9	13.5 ± 1.2
female g/dL (mean ± SD)	13.1 ± 0.9	12.5 ± 1.0	12.2 ± 0.9
Reference Values for Diagnosis			
male g/dL (mean – 2SD)	12.4	12.0	11.1
female g/dL (mean – 2SD)	11.3	10.5	10.4

TABLE 2. *Mean hematocrit levels in Japanese males and females and the criteria for anemia*

	(Japan Complete Book on Hematology, new edition) 20–59 years	(Chronological scientific) 60–69 years	70–79 years
male % (mean ± SD)	44.5 ± 2.9	42.0 ± 2.8	40.9 ± 3.6
female % (mean ± SD)	39.7 ± 2.6	37.6 ± 3.1	36.9 ± 2.9
Reference Values for Diagnosis			
male % (mean – 2SD)	38.7	36.4	33.7
female % (mean – 2SD)	34.5	31.4	31.1

criteria for anemia must be established, considering these factors.

2. The Hb value is employed in the criteria for anemia; however, we recommend that the Ht value should be additionally written.
3. In diagnosing anemia, various disorders causing anemia must be differentiated. Mean corpuscular volume (MCV) is a useful index.
4. Renal anemia is diagnosed when there is no disorder other than renal hypofunction as the cause of anemia.

1. General criteria for anemia

The reference values for both males and females for diagnosing anemia in Japanese individuals aged more than 60 years are lower than the values in Europeans and Americans.

1. Definition of anemia

Anemia is not a disease name but a condition in which the Hb level per blood unit volume is decreased. Hb plays a role in oxygen transport to each tissue; therefore, when anemia occurs, oxygen supply to tissues is reduced, and in vivo function is influenced in accordance with the severity of anemia.

2. Criteria

There is no textbook in which numerical criteria for anemia based on the results of measurement involving the Japanese are described. Therefore, we calculated the reference values for diagnosing anemia in reference to the average Hb/Ht values in the Japanese (Tables 1, 2)(1,2). Regarding the mean – 2SD (standard deviation) as the reference value for diagnosing anemia, there were gender/age-related differences, as shown in Tables 1 and 2. Furthermore, the general criteria for anemia described in the Guidelines for the Treatment of Renal Anemia in Europe (EDTA) (3) and the United States (NKF-K/DOQI) (4) are presented in Table 3. As shown in Tables 1 and 2, the reference values for diagnosing anemia in Japanese males and females aged more than 60 years are lower than the values in Europeans and Americans.

2. Differential diagnosis of anemia and examination items

In diagnosing anemia, various disorders causing anemia must be differentiated. In the differential diagnosis of anemia, the type of anemia should be classified into microcytic, normocytic, or macrocytic anemia based on MCV in clinical practice. It has been reported that renal anemia related to kidney disease is classified as normocytic or macrocytic anemia. The disorders differentiated using MCV are shown in Table 4.

Subsequently, the examination items necessary for differentiating individual diseases are summarized in Table 5; the items, including a peripheral blood test, parameters of iron metabolism, blood biochemistry, a serological test, bone marrow puncture, and vitamin/hormone tests, vary. All parameters do not have to be simultaneously determined; it is important to select the examination items in accordance with dis-

TABLE 3. *EDTA and NKF-K/DOQI criteria for anemia*

	Hb	Ht
Pre-menopausal women and pre-adolescent patients	<11 g/dL	<33%
Adult males and post-menopausal women	<12 g/dL	<37%

TABLE 4. *Differential diagnosis of anemia*

Microcytic	Iron-deficiency anemia, anemia of chronic disorders, sideroblastic anemia, thalassemia, and atransferrinemia
Normocytic	Renal anemia, hemolytic anemia, aplastic anemia, pure red cell aplasia, myelodysplastic syndrome, anemia of chronic disorders, and leukemia
Macrocytic	Renal anemia, megaloblastic anemia (vitamin B12 deficiency, folic acid deficiency), hepatopathy, hypothyroidism, aplastic anemia, myelodysplastic syndrome, and drug-related disorders in DNA synthesis.

orders to be differentiated. Measurement of the blood EPO level in the diagnosis of renal anemia is less significant.

3. Definition of renal anemia

Renal anemia is a condition in which there are no etiological factors for anemia other than renal hypofunction.

Renal anemia indicates a condition in which renal hypofunction-related reduction of production of EPO by the kidney makes it difficult to maintain an Hb level exceeding the reference value. In Japan, the reference values in accordance with gender and age, as shown in Tables 1 and 2, may be adequate. These reference values have limitations, but are sometimes indicated for evaluating preservative-phase renal failure and the state after the start of dialysis.

Renal hypofunction with a serum creatinine level of 2 mg/dL or more, or a creatinine clearance of less than 20–35 mL/min may lead to renal anemia (5–7). In patients with diabetic nephropathy, renal anemia occurs earlier than in patients with non-diabetic nephropathy. When creatinine clearance is less than 45 mL/min, renal anemia should be suspected.

To diagnose renal anemia, causative disorders other than renal hypofunction must be ruled out. In particular, renal anemia is most frequently complicated by iron-deficiency anemia.

CHAPTER II

Target hemoglobin value in rHuEPO therapy and the criteria for starting administration

1. We recommend that rHuEPO therapy in patients undergoing HD should target an Hb level of 10–11 g/dL (Ht: 30–33%) in blood samples collected in the supine position before HD at the beginning of the week (2 days after predialysis).
2. When the Hb level is less than 10 g/dL (Ht: less than 30%) at several examinations under a diagnosis of renal anemia, administration of rHuEPO should be initiated.
3. In relatively young patients with high activity levels, an Hb level of 11–12 g/dL (Ht: 33–36%) should be maintained. When the Hb level is less than 11 g/dL (Ht: less than 33%) at several examinations, administration of rHuEPO should be initiated.

1. Background of rHuEPO therapy

Most studies, of which the results were employed as the database for establishing the guidelines for renal anemia treatment in Europe (EDTA) (8) and the United States (NKF-K/DOQI) (9), in which the optimal Hb (Ht) value in rHuEPO therapy is presented, involved patients undergoing HD; there were few data on patients undergoing CAPD or those with preservative-phase chronic renal failure. In Europe and the United States only the target value in rHuEPO therapy has been established, however, there is no evidence that the target value in patients undergoing HD applies to that in patients undergoing CAPD or those with preservative-phase chronic renal failure. Therefore, our guidelines involved only patients undergoing HD.

On the peripheral blood test, the Hb level was measured; the Ht value was calculated from Hb and MCV. As MCV depends on various factors, the Hb level is employed as a parameter of anemia in the EDTA and NKF-K/DOQI guidelines. However, in 'a survey on the current status in Japan' conducted by the JSDT, and in the results of the survey described

TABLE 5. *Examination items for the differential diagnosis of anemia*

1.	RBC, Hb, Ht, MCV, MCH, and MCHC
2.	Reticulocytes
3.	Parameters of iron metabolism (Fe, UIBC, ferritin, and TSAT)
4.	Leukocyte count, WBC fraction, and platelet count
5.	Occult blood in stool
6.	Blood biochemistry and protein fraction
7.	CRP
8.	Bone marrow test
9.	Vitamin B12 and folic acid
10.	Coombs' test and haptoglobin
11.	Blood aluminum level
12.	Thyroid function
13.	Parathyroid function (intact PTH)
14.	Others

TSAT (%) = [serum iron (g/dL)/total iron binding capacity (g/dL)] × 100.

CRP, C reactive protein; Hb, hemoglobin; Ht, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PTH, parathyroid hormone; RBC, red blood cell; UIBC, unsaturated iron binding capacity; WBC, white blood cell.

TABLE 6. *Influence of the hematocrit (Ht) value prior to hemodialysis (HD) at the end of 1995 on the 5-year survival rate (corrected by age, gender, underlying disease, Kt/V urea, and percent weight loss)*

Ht value prior to HD (%)	Relative risk (95% confidence interval)	*P*-value
<24	1.714 (1.610–1.820)	0.0001
24–27	1.219 (1.159–1.280)	0.0001
27–30	1.026 (0.980–1.070)	0.2722
30–33	1.000 (control)	control
33–36	1.112 (1.050–1.178)	0.0003
36–39	1.254 (1.156–1.362)	0.0001
>39	1.306 (1.185–1.440)	0.0001

below, the Ht value was used as a parameter of anemia. Therefore, we employed the Hb level as the main parameter, as used in the EDTA and NKF-K/DOQI guidelines, and the Ht value was additionally written. In the future, the Hb level should be employed in all surveys/studies. Accurately, the Hb level (g/dL) does not always correspond to one-third of the Ht value (%); however, there is no clinically significant error, and this calculation method was employed, as performed in Europe and the United States.

In the EDTA and NKF-K/DOQI guidelines, the target Hb level is established as 11–12 g/dL or more, based on the results of studies in which the parameters included the survival rate, morbidity, left ventricular cardiac muscle weight, QOL, physical activities, frequency of admission (days), recognition ability, metabolic function, and sleep pattern (8,9).

There is a race-related difference in the normal Hb (Ht) level between the Japanese and Europeans/Americans; the Hb (Ht) value is slightly lower in elderly Japanese individuals (refer to Chapter I). However, there are few studies providing satisfactory data for establishing the target Hb (Ht) value in rHuEPO therapy in the Japanese. The results of statistical surveys performed by the JSDT every year have confirmed that the best Ht value is 30–35% when investigating the influence of independent factors on the 1-year survival rate. However, these surveys evaluated only the short-term prognosis, the 1-year survival rate, and the interval of Ht is large (5%), which is a limitation.

Therefore, utilizing the JSDT statistical survey material, we stratified the Ht value at the end of 1995 (55 855 patients including those without rHuEPO) at 3-percent intervals, as performed in Europe and the United States, and examined the influence on the 5-year survival rate. Even after the Ht value was corrected by age, gender, underlying disease, weight gain, and Kt/V, the relative risk in patients with an Ht value of 27–33% was lowest (Table 6)(unpublished data, 2003). With respect to age and underlying disease, the survival rate was highest in patients with an Ht value of 30–33%, although there were slight differences.

In a retrospective study, Hirasawa et al. investigated the 3-year mortality rate based on the mean Ht values at 3 points in 2654 patients undergoing maintenance dialysis and receiving rHuEPO in 22 hospitals in Japan. They evaluated the prognosis with respect to the Ht value corrected by age, gender, underlying disease, complications, and albumin level, and reported that the survival rate was highest in patients with an Ht value of 30–33% (Table 7)(10).

TABLE 7. *Influence of the hematocrit value/patient characteristics on the 1-year and 3-year mortality rates*

	1-year mortality rate			3-year mortality rate		
Background factor	RR	95% CI	*P*-value	RR	95% CI	*P*-value
Group 1 (Ht ≥ 36%)	0	0	0.9694	0.915	0.405–2.072	0.8321
Group 2 (33% ≤ Ht <36%)	0.605	0.320–1.146	0.1231	1.111	0.816–1.514	0.5036
Group 3 (30% ≤ Ht <33%)	0.447	0.290–0.689	0.0003	0.677	0.537–0.855	0.001
Group 4 (27% ≤ Ht <30%)	1					
Group 5 (Ht < 27%)	1.657	1.161–2.367	0.0054	1.604	1.275–2.019	<0.0001
Age: 1-year increase	1.029	1.016–1.043	<0.0001	1.048	1.039–1.056	<0.0001
Gender: female	0.85	0.620–1.167	0.3159	0.758	0.629–0.913	0.0036
Underlying disease Diabetic nephropathy	0.958	0.671–1.368	0.815	1.354	1.114–1.647	0.0024
Complications						
Heart disease	1.224	0.883–1.696	0.2256	1.596	1.319–1.932	<0.0001
Occlusive arteriosclerosis	1.281	0.844–1.944	0.2456	1.639	1.302–2.063	<0.0001
Cerebrovascular disorders	1.683	1.142–2.480	0.0085	1.522	1.211–1.913	0.0003
Digestive disorders	1.190	0.870–1.628	0.2759	0.907	0.753–1.093	0.3051
Hepatic/biliary system disorders	1.438	0.978–2.117	0.0651	1.264	0.997–1.603	0.0528
Cancer	1.725	0.943–3.156	0.0768	2.716	1.910–3.862	<0.0001
Alb <3.5 g/dL	1					
≥3.5 g/dL	0.424	0.307–0.585	<0.0001	0.603	0.501–0.726	<0.0001

95% CI, 95% confidence interval; RR, relative risk; Alb, albumin.
This table is quoted from the study described by Hirasawa et al. (10).

TABLE 8. *Differences between the days of blood collection. (Comparison of the hematological data between Monday and Wednesday of the same week in 247 patients undergoing dialysis on Monday, Wednesday and Friday)*

	Monday	Wednesday	Difference
BW (kg)	53.1 ± 0.7	52.6 ± 8.9	0.6
Hb value (g/dL)	10.4 ± 1.0	10.5 ± 1.3	0.15
Ht value (%)	32.3 ± 3.5	32.6 ± 4.4	0.36
TP (g/dL)	6.7 ± 0.5	6.7 ± 0.5	0.05

BW, body weight; Hb, hemoglobin; Ht, hematocrit; TP, total protein.

These results suggest that the target Hb level in rHuEPO therapy should be 10–11 g/dL (Ht: 30–33%). However, in the analysis regarding the 5-year survival rate using the statistical data collected by the JSDT, the relative risk (0.78) in patients with an Ht value of 33–36% was lower than that with 30–33% among the patients aged 35–45 years, although there was no significant difference; therefore, we recommended that the target Hb level should be 11–12 g/dL (Ht: 33–36%) in young patients with high activities in whom the risk of arteriosclerotic lesions is low.

Our target value differed from the target Hb (Ht) values in the EDTA and NKF-K/DOQI guidelines, possibly because there were differences in the day of the week on which blood was collected and the position at blood collection, in addition to the race difference. To demonstrate this hypothesis, two additional studies were conducted.

In the JSDT survey, the data on Ht at the beginning of the week were employed in most patients, whereas the results of blood collection on the middle day of the week were employed in Europe and the United States; the difference in the rate of weight gain may have influenced the results. Therefore, we compared the peripheral blood data between Mondays and Wednesdays in 247 patients undergoing HD three times a week (Monday, Wednesday, and Friday) in a single hospital. The Ht value on Mondays corresponded to 99.1% of that on Wednesdays (Table 8; unpublished data, 2003).

It is also known that the position at blood collection influences the Ht value. A study in Japan has reported that the Ht value in patients undergoing HD was more markedly decreased in the supine position compared to that in healthy adults (11). In Europe and the United States, most patients undergo HD in the sitting position on a chair-bed, whereas in Japan, most patients undergo HD in the supine position; the position at blood collection differs. Therefore, in 99 patients undergoing HD three times a week in four hospitals, we compared the data on peripheral blood collected in the sitting position immediately after entering the room with the data on that collected about 10 min after the supine position was assumed. The Ht value when blood was collected in the supine position was 94.3% of that when blood was collected in the sitting position (Table 9; unpublished data, 2003).

When calculating the above two factors, the Ht value (33–36%) in Europe and the United States corresponded to that of 30.8–33.6% in Japan, supporting the study results quoted regarding the influence on the prognosis in Japan.

However, the above studies were retrospective studies based on transient Ht values, and only the prognosis was regarded as the endpoint. To establish an accurate target Hb (Ht) value, a large-scale prospective randomized controlled study should be conducted in the future, regarding QOL as the endpoint. Furthermore, no study has investigated differences in the improvement rating for anemia among different dialysis procedures, such as hemofiltration and hemodiafiltration, and the widespread use of these dialysis procedures may influence the target Hb (Ht) value. Therefore, this recommended value must be regularly reviewed.

CHAPTER III

Diagnosis and treatment of iron deficiency

1. Patients undergoing HD lose approximately 2 g/year of iron due to blood remaining in the dialyzer and blood collection tests. Therefore, iron deficiency readily occurs. To diagnose iron deficiency, the transferrin saturation (TSAT) and serum ferritin level are used as standard markers. The guidelines for iron overload in Europe and the

TABLE 9. *Comparison of the hematocrit value between the sitting position and the supine position in patients undergoing hemodialysis*

Results	Sitting position	Supine position
Cr value	10.9 ± 2.8	10.9 ± 2.8
BUN	74.4 ± 12.4	74.0 ± 12.2
Hb value	10.7 ± 1.0	10.1 ± 0.9 (94.4%)
Ht value	33.2 ± 3.0	31.3 ± 2.9 (94.3%)
TP	6.7 ± 0.5	6.3 ± 0.5 (94.0%)

Examination in Osaka prefecture Hospital and three other hospitals.

Examination was conducted in 99 patients with little residual renal function who were undergoing hemodialysis three times a week in four hospitals, and from whom informed consent was obtained. We collected blood via the venous route in the sitting position immediately after arrival, and via the arterial route about 10 minutes after they were placed in the supine position. The values were compared.

BUN, blood urea nitrogen; Cr, creatinine; Hb, hemoglobin; Ht, hematocrit; TP, total protein.

United States can not be readily recommended for the Japanese.
2. An iron preparation should be slowly administered via the dialysis circuit at the end of dialysis. The frequency of administration is a total of 13 times (every point of dialysis) or once a week for 3 months. The presence of conditions contraindicating iron preparations must be considered.

1. Diagnosis of iron deficiency

The criteria for iron deficiency include a TSAT of 20% or less and a serum ferritin level of 100 ng/mL or less.

1. Definition of iron deficiency and iron overload

Iron deficiency and iron overload are closely associated with hematopoiesis. In addition, the in vivo state of iron must be evaluated with respect to its role and distribution (12).

Patients undergoing HD lose approximately 2 g/year of iron due to blood remaining in the dialyzer and blood collection tests. In those in whom hematopoiesis is maintained, iron deficiency occurs unless iron supplements are given. To achieve the effects of EPO, iron supply meeting the synthesis of Hb must be maintained so that hematopoiesis reaches a maximum (13–15).

In addition, iron deficiency induces allotriogeusia and deformity of the nail, and iron overload causes hemosiderosis and infection-prone features; therefore iron deficiency must be avoided.

2. Diagnosis of iron deficiency

In evaluating iron deficiency, MCV is routinely used as a simple diagnostic marker. However, the sensitivity and specificity of MCV are insufficient. Therefore, the criteria for iron deficiency include a TSAT of 20% or less, a serum ferritin level of 100 ng/mL or less, a reticulocyte Hb level of less than 32.2 pg, and a decrease in MCV over 4–5 months. Among these parameters, health insurance is not indicated for the reticulocyte Hb level, and TSAT and serum ferritin levels are used as standard markers of iron deficiency.

TSAT: Transferrin saturation

TSAT(%) = [serum iron (μg/dL) × total iron binding capacity (μg/dL)] × 100

3. Diagnosis of iron overload

To prevent and relieve the side-effects of iron preparations, iron overload must be adequately diagnosed. In the EDTA and NKF-K/DOQI guidelines (8,16,17), it is described that an Hb level of 11–12 g/dL can be maintained by continuous administration of iron preparations when the values of TSAT and serum ferritin are less than 50% and less than 800 ng/mL, respectively. However, we cannot recommend that iron preparations should be continuously administered until the TSAT and serum ferritin values reach approximately 50% and 800 ng/mL, respectively, considering the risk of iron overload (18–20).

The sensitivity and specificity when the TSAT and serum ferritin level are employed to diagnose iron overload are poor (21); the simple diagnosis of iron overload is impossible (Table 10).

Thus, as a safer method of administration, we recommend not continuous administration of iron preparations for maintaining the target ranges of specific iron parameters (22,23), but transient administration of iron preparations in the presence of iron deficiency and discontinuation after improvement (24–26).

2. Administration of iron preparations

Iron preparations should be intravenously injected at a low rate at the end of dialysis. The frequency of

TABLE 10. *Sensitivity and specificigy of markers of iron deficiency/iron overload*

	Sensitivity/Specificity	Medical insurance point/time	Remarks
Parameters of iron deficiency			
TSAT (%) (<20%)	Control	37 point/1 hour	
Ferritin (ng/ml) (<100 ng/ml)	84.2%/31.4%	150 point/1 hour	A parameter of stored iron
HYPO (%) (<2.5%)	39.1%/35.6%	/10 min	A parameter of the erythrocyte level
(<10%)	86.5%/20.6%		
CHr (pg) (<32.2 pg)	76.5%/73.4%	unapproved/10 min	A parameter of the erythrocyte level
sTfR (mg/ml) (>1200 mg/ml)	40.5%/33.9%	unapproved/depending on assay kit	This parameter reflects iron deficiency and cell proliferation
Parameters of iron overload			
TSAT (%) (>50%)	Control	37 point/	
Ferritin (ng/ml) (>800ng/ml)	46.7%/99.4%	150 point	A parameter of stored iron
HYPO (%) (>10%)	0%/90%		A parameter of the erythrocyte level
CHr (pg) (>33 pg)	61.5%/65%	unapproved/	A parameter of the erythrocyte level
sTfR (mg/ml) (<1000 mg/ml)	52.4%/36.2%	unapproved/	

administration is a total of 13 times (every point of dialysis) or once a week for 3 months.

1. Selection of iron preparations and the administration route

Iron preparations are classified into oral preparations and intravenous injection preparations. In addition, subcutaneous injection is recommended in Europe and the United States; however, it is not approved in Japan. Administration of an excessive dose of these preparations causes iron overload, therefore close monitoring is needed.

To manage a rapid increase in iron demand for hematopoiesis related to administration of rHuEPO, intravascular administration should be performed. As iron preparations for intravenous injection, saccharated ferric oxide (24), chondroitin sulfate/iron colloid solution (25), and cideferron (26) are commercially available in Japan.

2. Dose of iron preparations and the frequency of administration

When iron deficiency is diagnosed according to the above criteria, and there are no contraindications for iron preparations (shown below), chondroitin sulfate/iron colloid solution at 40 mg is administered 13 times (every point of dialysis) or once a week for 3 months. At the end of dialysis, these agents are slowly administered via the venous side of the dialysis circuit. Immediately after administration, intravenous injection preparations rapidly cause shock in some patients (27–32). In particular, for the initial dosing, a half-dose diluted should be slowly administered under close monitoring, and we recommend that patients should be monitored for 1 h after administration to confirm the absence of hypersensitivity.

The above examination is repeatedly performed 2 weeks after the end of administration. When iron deficiency is observed, iron preparations should be repeatedly administered, as described above.

3. Contraindications for administration of iron preparations

Even when physicians consider that iron preparations are indicated, administration should be discontinued, or these preparations should be administered after establishing strategies in the following cases:

1. A history of iron preparation-related anaphylaxis.
2. A medical history/symptoms suggesting iron overload, a history of massive blood transfusion, hemosiderosis (33), hemochromatosis, or siderosis (34), is present.
3. The presence of infection. It has been reported that administration of iron preparations causes/exacerbates bacterial infection and mycosis (35).
4. Viral hepatitis. In the presence of iron deficiency, liver dysfunction or the responsiveness to interferon improves, and administration of iron preparations may lead to adverse reactions (36).

CHAPTER IV

Administration method of rHuEPO — Administration route/dose

1. Concerning the administration route, the incidence of PRCA associated with rHuEPO-related production of EPO autoantibody was high in patients in whom rHuEPO was subcutaneously injected. Therefore, we recommend intravenous injection via the dialysis circuit.
2. The initial dose for intravenous injection should be 1500 units, which is administered three times a week. When anemia-improving effects are not achieved, the dose may be increased to 3000 units.
3. The dose and the frequency of administration should be determined based on the target level of improvement in anemia and the velocity at which this agent improves anemia; the current upper limits of the dose/frequency of administration must be reviewed.

1. Administration route of rHuEPO — Intravenous injection and subcutaneous injection

As a rule, rHuEPO should be intravenously injected via the dialysis circuit at the end of dialysis in patients undergoing HD.

In Japan, the administration route of rHuEPO is restricted to intravenous injection in patients undergoing HD in the medical insurance system proposed by the Science Research Group, Ministry of Health and Welfare (Director: Y. Hirasawa) (37), in 1990. Subcutaneous injection is approved only for patients undergoing CAPD and those with preservative-phase chronic renal failure. In Europe and the United States, many clinical studies have compared intravenous injection with subcutaneous injection, and based on the results, it is indicated that subcutaneous injection is more advantageous with respect to the anemia-improving/improvement-maintaining effects of rHuEPO and medical financial issues (38–50).

Based on these results, it is recommended that subcutaneous injection should be performed not only in patients undergoing CAPD and those with preservative-phase chronic renal failure but also in patients

undergoing HD as in the Guidelines for the Treatment of Renal Anemia in Europe (EDTA) (8,51) and the United States (NKF-K/DOQI) (52). In Europe, subcutaneous injection was applied in only 30% of the patients at the beginning of 1990; however, thereafter, the percentage reached approximately 90%, and autoinjection was approved. However, currently, intravenous injection is performed in most patients, in consideration of the onset of pure red cell aplasia (PRCA). In the United States, which presents a different case to that of Europe, the rate at which intravenous injection is performed remains high mainly due to the simple injection procedure and subcutaneous injection is indicated for approximately 10% of patients (53).

The greatest merits of subcutaneous injection are a decrease in the dose and saving of health expenditure. The disadvantages of subcutaneous injection include a low rate of bioavailability (approximately 20% of that for intravenous injection), a sebum thickness-related dispersion in the absorption rate, and topical pain at the injection site. The pharmacokinetic characteristic of subcutaneous injection is that the blood level of EPO remains low, at approximately 100 mU/mL, for a long duration (high time-averaged plasma concentration), leading to anemia-improving effects as potent as those of intravenous injection, despite a low rate of bioavailability (54).

Usually, rHuEPO must be administered two to three times a week. A study has reported that the femoral region with high absorption efficiency is most appropriate for subcutaneous injection; however, there is no evidence to support this. It has been indicated that the injection site must always be changed. However, subcutaneous injection-related pain is severe, and in patients who can not endure it, intravenous injection should be performed.

Intravenous injection targets erythroblasts via the complete actions of rHuEPO. As a pharmacokinetic characteristic, the blood level of EPO rapidly increases immediately after administration, but then rapidly decreases; the trough value is lower than that when the subcutaneous injection method is employed. Recently, it has been indicated that this characteristic may etiologically contribute to the clinical rHuEPO resistance; Rice et al. (55) reported that a rapid decrease in the blood level of EPO after intravenous injection induced apoptosis (neocytolysis) of immature erythrocytes released by the bone marrow.

Since Bommer et al. (38) initially reported the usefulness of rHuEPO in 1991, 36 studies (involving 2028 patients) in Europe and the United States have compared the usefulness of rHuEPO between intravenous injection and subcutaneous injection. Only three of these studies reported that there was no difference between the two injection procedures, whereas most studies indicated the usefulness of subcutaneous injection. In Japan, two studies have investigated the usefulness of rHuEPO (56,57). In a clinical trial of the recombinant human erythropoietin SNB-5001 involving patients undergoing HD, Koshikawa et al. (56) compared the effects on anemia among three groups, two subcutaneous injection groups (6000 or 12 000 units, once a week) and an intravenous injection group (3000 units, three times a week), and reported that the effects on anemia were most marked in the subcutaneous injection group (12 000 units, once a week). Maeda et al. (57) investigated the total dose when intravenous injection was switched to subcutaneous injection in patients undergoing HD, and reported that subcutaneous injection decreased the total dose by approximately 38%. Other studies have also indicated that a switch from intravenous injection to subcutaneous injection decreased the dose by approximately 30%. In a meta-analysis involving 27 prospective studies (total number of patients, 916), Besarab et al. (49) reported that the subcutaneous dose necessary for achieving similar anemia-improving effects was approximately 30% of the intravenous dose, and emphasized that health expenditure can be saved by approximately 30%.

Thus, with respect to the administration method of rHuEPO, it has been emphasized that subcutaneous injection is more advantageous; however, after 1998, secondary PRCA related to formation of an anti-erythropoietin antibody developed in patients treated with EPREX (epoetin α: Johnson & Johnson Pharmaceutical Research & Development, LLC, La Jolla, CA, USA) in Europe (58). In patient blood, a neutralizing antibody against intrinsic EPO was detected, and bone marrow hematopoiesis was markedly inhibited; therefore, blood transfusion was required. Recently, the use of immunosuppressive agents has been considered. According to an announcement issued by Johnson & Johnson Inc., the data on 188 patients, including those under a tentative diagnosis, had been collected (as of late October 2002). EPREX had been administered to 106 (56%) of these patients (59). The incidence of PRCA in the total number of patients treated with rHuEPO is extremely low throughout the world; however, it has been confirmed that rHuEPO induces an adverse reaction related to antibody production common among protein preparations, which was initially expected when this agent was developed.

It is generally known that production of antibodies against protein preparations is high in patients who frequently receive subcutaneous injection (60). A study has reported that the incidence of rHuEPO-related PRCA in patients receiving subcutaneous injection was 33 times higher than that in those receiving intravenous injection (59). The pathogenesis of PRCA remains to be clarified; it is speculated that the state in which the preparation is transported, storage of the preparation (in a refrigerator) by patients performing autoinjection, and agitation-related enhancement of antigenicity may be involved. An accurate method for detecting antibodies is being developed. Based on the above background, Johnson & Johnson Inc. recommended that subcutaneous injection should be switched to intravenous injection concerning the administration method of EPREX (9).

Since the clinical application of rHuEPO, the accurate anemia-improving effects of rHuEPO have been demonstrated; however, the necessity of decreasing the dose has been emphasized with respect to medical financial issues in Europe and the United States, and subcutaneous injection has been recommended. However, as PRCA related to production of an antibody against rHuEPO has developed, the risk of subcutaneous injection is indicated.

Epoetin α and epoetin β, which are commercially available in Japan, have been reported to cause PRCA. Considering this issue, intravenous injection, as currently performed, may be safe. We can not rule out the possibility that more adverse reactions related to production of antibodies against rHuEPO preparations could occur; close monitoring and the development of an accurate method for detecting antibodies are needed.

2. Dose of rHuEPO

To patients undergoing HD, rHuEPO at an initial dose of 1500–3000 units should be intravenously injected three times a week. During administration, monitoring should be performed so that the rate of increase of the Hb level does not exceed 0.3–0.4 g/dL (Ht: 1%) per week.

When the rate of increase of the Hb level is less than 1 g/dL (Ht: 3%) 4 weeks after the start of administration, intravenous injection of 3000 units of rHuEPO should be continued at a frequency of three times a week. When the desired effect is not obtained, etiological factors should be investigated, considering rHuEPO resistance.

With respect to the dose of rHuEPO, the Science Research Group, Ministry of Health and Welfare (37), as described above, published the therapeutic guidelines; the target Ht value was established as 30% in patients undergoing HD with an Ht value of less than 25%, and it is recommended that rHuEPO at an initial dose of 1500 units should be intravenously injected three times a week. When the rate of increase in Ht is less than 3% 4 weeks after the start of administration, the dose should be increased to 3000 units (three times a week). In addition, when the rate of increase of Ht is less than 3% after 4 weeks of follow-up, the dose should be increased to 6000 units (three times a week). It is proposed that when rHuEPO intravenously injected at 6000 units three times a week does not achieve the target value, etiological factors should be investigated, considering rHuEPO resistance. However, intravenous injection of rHuEPO at 6000 units performed three times a week exceeds the limit established in the current medical insurance system; clinical application is difficult.

After Ht reaches the target value in all stages, the dose should be decreased to one-third to one-half, and employed as the maintenance dose. In Japan, it is described in the package inserts for rHuEPO preparations that rHuEPO at an initial dose of 3000 units (150–180 units/kg/week) should be intravenously injected at the end of HD (three times a week). However, the guidelines established by the Science Research Group, Ministry of Health and Welfare, are applied, and administration is started at 1500 units in many patients. Generally, this initial dose is low, and when the effects are not considered sufficient by monitoring the rate at which rHuEPO improves anemia, the dose is gradually increased. In Japan, the incidence of serious side-effects, such as hypertensive encephalopathy-like convulsive attacks, has been lower than that in Europe and the United States since the start of clinical application. The suggestion that administration should be initiated at a low dose, which was proposed by the Science Research Group, Ministry of Health and Welfare, may have contributed to this result.

In Europe and the United States, generally, the dose per body weight has been determined, and administration has been initiated at a high dose. However, serious side-effects, such as convulsive attacks, have been increasingly reported, and to prevent these side-effects, it has been proposed that doses for subcutaneous injection and intravenous injection should be 80–120 units/kg/week and 120–180 units/kg/week, respectively, in the Guidelines for the Treatment of Renal Anemia in Europe (EDTA) (51) and the United States (NKF-K/DOQI) (52). These doses correspond to 6000 units for subcutaneous injection and 9000 units for intravenous

injection, and do not markedly differ from the doses in Japan. In many children, especially those aged less than 5 years, a high dose is required, and the dose is reported to be approximately 300 units/kg/week.

The dose of rHuEPO must be determined after correcting the target value or rate in accordance with the patient condition. Based on the results of dosimetry studies in clinical trials, it is emphasized that the rate of increase in the Hb level per week should be 0.3–0.4 g/dL (Ht: 1%) or less; exacerbation of hypertension or elevation of blood pressure occurs when the rate of increase in Ht per week is 1% or more, and many patients require the start of hypotensive treatment or increase of hypotensive agents. In addition, the Ht value before administration is an important factor; in patients with a lower Ht value, a higher dose is required to achieve rapid correction. It must be considered that rHuEPO improves anemia more rapidly than expected in some patients, along with improvement in uremia, at the start of dialysis. During administration, it is important to prevent adverse reactions, such as the appearance of symptoms represented by headache, elevation of blood pressure, exacerbation of hypertension, and blood access occlusion.

CHAPTER V

Resistance to EPO (low responsiveness)

1. In Japan, patients in whom EPO is intravenously injected at 3000 units three times a week in the absence of iron deficiency where anemia is not improved are regarded as resistant to EPO from the perspective of medical insurance practice; however, this criterion lacks scientific/medical grounds.
2. In most patients we encounter, EPO resistance is associated with iron deficiency. In the absence of iron deficiency, other etiological factors for the resistance should be investigated. In particular, the most serious complication is PRCA related to the appearance of an anti-EPO antibody.
3. It is known that a deficit in components essential for hematopoiesis, other than iron, attenuates the effects of EPO in some patients.

1. Definition of low responsiveness

Usually, EPO resistance is not absolute but relative. It should be expressed as 'low responsiveness to EPO'.

There is no accurate definition of EPO resistance. Patients undergoing HD in whom EPO intravenously injected at 3000 units three times a week (9000 units/week) does not improve anemia are regarded as resistant to EPO. This is because the maximum dose per week in patients undergoing HD is established as 9000 units in the medical insurance system in Japan, and the above definition is not based on medical grounds. In patients weighing 50–60 kg, this dose corresponds to 150–180 units/kg/week.

When EPO is intravenously injected, 96% of patients treated at 450 units/kg/week achieve the target Hb (Ht) value within 4–6 months (61); therefore, in the NKF-K/DOQI guidelines, patients without effective hematopoietic reaction to a higher dose of EPO are regarded as resistant to EPO. This dose (450 units/kg/week, intravenous) corresponds to 300 units/kg/week subcutaneously injected. When EPO is subcutaneously injected, patients who do not respond to EPO at 300 units/kg/week are regarded as resistant to EPO.

In the EDTA guidelines, patients in whom subcutaneous injection at 300 units/kg/week (approximately 20 000 units/week) or more does not achieve the target Hb (Ht) value or those in whom the target Hb (Ht) value can not be maintained are regarded as resistant to EPO (62). Usually, the resistance is not absolute but relative; it should be expressed as 'low responsiveness to EPO'. It is described that the resistance depends on uncertain factors in individuals and the initial dose.

No criteria for EPO resistance in patients with preservative-phase chronic renal failure are presented in the EDTA or NKF-K/DOQI guidelines.

2. Etiological factors for low responsiveness to EPO

The most important etiological factor for low responsiveness to EPO is absolute/relative iron deficiency. Other factors are also known.

In 90% of patients receiving a sufficient amount of iron supplements, EPO at a dose markedly lower than the EPO level that is considered the criterion for low responsiveness may achieve hematopoiesis (61). Briefly, the most important etiological factor for low responsiveness to EPO is absolute/relative iron deficiency. Therefore, in patients who do not respond to EPO in the absence of iron deficiency, the factors described in Tables 11 and 12 should be investigated.

Blood loss for a long period induces iron deficiency. In the presence of inflammation including infectious disease and chronic rejection in transplanted organs, inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL-6), with an increase in the count, inhibit initial maturation of erythrocyte precursors. Parathyroid hormones inhibit hematopoiesis, and fibrous ostitis involves the bone marrow, influencing hematopoie-

TABLE 11. *Major etiological factors for low responsiveness to erythropoietin (EPO)*

Chronic blood loss of the digestive tract/genital organs (63)
Infectious disease (blood access/peritoneal access infection), inflammation, surgical infectious disease, tuberculosis, SLE and AIDS (64–67)
Chronic rejection in graft (68)
Severe hyperparathyroidism (fibrous ostitis) (69)
Aluminum toxication (70–73)
Folic acid/vitamin B12 deficiency (74,75)
Multiple myeloma (76,77)
Other malignant tumors (78)
Hemolysis (79)
Hemoglobinopathy (α,β thalassemia) (80,81)/sickle cell anemia (82)
Hypersplenism (83)
Appearance of an anti-EPO antibody (58)

SLE, systemic lupus erythematosus.

sis. Aluminum inhibits the synthesis of hemoglobin, causing microcytic hypochromic anemia. Folic acid and vitamin B12 are essential for production of erythrocytes. It can not be concluded that there is no response of multiple myeloma to rHuEPO; however, there are marked individual differences in low responsiveness, and the reason is unclear. Patients with other malignant tumors require a larger amount of rHuEPO in comparison to that required for anemia treatment in patients with chronic renal failure; however, in this case, it is also speculated that cytokines such as TNF-α may be involved.

Hemolysis mechanically and immunologically occurs, leading to low responsiveness to EPO. Patients with hemoglobinopathy require long-term massive therapy with rHuEPO. In patients with hypersplenism of the spleen, retention of erythrocytes in the spleen is observed, and improvement in anemia is not achieved in some patients even when the reticulocyte count is increased. The most serious condition is pure red cell aplasia (PRCA) at the appearance of an anti-EPO antibody. Some studies have indicated that angiotensin converting enzyme inhibitors reduce the responsiveness to EPO, whereas others have objected to this hypothesis. Carnitine is involved in the synthesis of fatty acid, an erythrocyte membrane component. In many patients undergoing dialysis, the presence of carnitine deficiency increases the rHuEPO requirement.

It is unclear whether insufficient dialysis and treatment using a dialysis membrane with low bioadaptability are the direct causes of low responsiveness to EPO. In contrast, it is known that slow dialysis for a long duration or continuous night dialysis improves anemia. Malnutrition is often observed in patients undergoing HD; there is a correlation between the albumin level and the Hb level. Furthermore, hypoalbuminemia is associated with inflammation. In addition, hypoalbuminemia is closely associated with a lack of carnitine/vitamin intake and zinc deficiency in the presence of malnutrition.

It is assumed that vitamin C mobilizes stored iron; a study has reported that vitamin C reinforces the actions of EPO. Vitamin E may reinforce the effects of EPO via antioxidant actions. It is known that anemia develops in patients with zinc deficiency. In many patients undergoing HD, the serum level of zinc is low. A study has reported that administration of zinc facilitated decreasing the dose of rHuEPO.

CHAPTER VI

Blood transfusion in patients with renal failure

1. The use of rHuEPO/iron preparations has decreased the frequency of blood transfusion in patients with renal failure. However, erythrocyte transfusion is still required under restricted conditions.
2. In patients who may undergo transplantation, sensitization with MHC antigen should be minimized using a leukocyte-removing filter.

1. Indications for blood transfusion

Erythrocyte transfusion should be performed only in a state in which improvement of anemia is reversible.

Improvement of dialysis efficiency related to improvement of dialysis technique, decreased blood loss during dialysis, and the appropriate use of rHuEPO/iron preparations has markedly improved renal anemia, decreasing the frequency of blood transfusion in patients with renal failure. However, erythrocyte transfusion is still required under restricted conditions. In the future, the necessity will persist. Erythrocyte transfusion should be performed only in a state in which improvement of anemia is reversible, i.e. prior to blood transfusion. Whether blood transfusion may improve some sign or clinical symptom must be carefully evaluated (92).

Erythrocyte transfusion is indicated for the following cases (Table 13):

TABLE 12. *Suspected etiological factors for low responsiveness to erythropoietin (EPO)*

Administration of ACE inhibitors (84,85)
Carnitine deficiency (86)
Insufficient dialysis (87)
Undernutrition (88)
Vitamin C deficiency (89)
Vitamin E deficiency (90)
Zinc deficiency (91)

ACE, angiotensin converting enzyme.

TABLE 13. *Representative patients undergoing dialysis and requiring erythrocyte transfusion*

Severe anemia patients with signs/symptoms specific to anemia
Patients with acute blood loss associated with unstable hemodynamics
Patients with severe angina pectoris
Intraoperative patients with a large volume of blood loss
Patients with low responsiveness to rHuEPO in the state of blood loss in which the hemoglobin level is decreased to the risk value

rHuEPO, recombinant human erythropoietin.

2. Cautions for blood transfusion

Blood transfusion causes side-effects in some patients.

In patients undergoing HD, blood transfusion is avoided because sensitization with MHC antigen, blood transfusion reaction, viral and parasite infection, and blood transfusion-related iron overload/hemosiderosis may occur. In addition, another reason is that the anemia-improving effects persist for a short period.

In particular, when blood transfusion is required in patients who may undergo transplantation or in those who are waiting for transplantation, countermeasures for minimizing sensitization with MHC antigen, such as the use of a leukocyte-removing filter, should be taken.

When surgery that may require blood transfusion is scheduled, administration of rHuEPO for achieving hematopoiesis and blood collection/storage are intentionally performed preoperatively, and autologous blood transfusion is performed during surgery in patients without dialysis. In the future, when autologous blood storage is approved for patients undergoing HD, the current reference dose of rHuEPO should be changed.

CHAPTER VII

Side-effects and concomitant symptoms of rHuEPO

1. The side-effects of rHuEPO include hypertension, thrombosis/embolism, and PRCA. These side-effects should be considered.

Since the clinical application of rHuEPO in 1990, many side-effects/concomitant symptoms have been reported. Among these, we introduce important side-effects supported by the literature at a high evidence level (Table 14).

1. Elevation of blood pressure

A rapid increase in the Hb (Ht) level induces hypertension.

Elevation of blood pressure is a representative concomitant symptom related to rHuEPO. The incidence of elevation of blood pressure, including hypertension, is approximately 3–7% according to the trial data and post-marketing clinical results in Japan, lower than that (20–30%) in other countries. However, a study has indicated that the incidence was 35.6% in a specific number of subjects (93).

The etiology of elevation of blood pressure is speculated to be as follows: there is no reduction of cardiac output, although correction of a low tissue oxygen concentration related to improvement of anemia increases peripheral vascular resistance via contraction of dilating peripheral blood vessels and enhancement of blood viscosity. Therefore, the above factor is latent in patients with a family/medical history of hypertension, and elevation of blood pressure readily occurs according to some investigators (94). In addition, many hypotheses have been proposed: resetting of the relationship between body fluid volume and peripheral vascular resistance related to improvement in anemia, the involvement of pressor substances such as endothelin, and enhancement of the responsiveness to pressor substances such as angiotensin.

To prevent hypertension, it has been recommended that anemia should be gradually corrected by maintaining a slow rate of improvement, considering elevation of blood pressure. As the reference rate at which rHuEPO improves anemia, it is proposed that the rate of increase in the Hb level should be 0.3–0.4 g/dL (Ht: 1%) or less. In particular, administration should be carefully performed in patients with a history of hypertension, considering elevation of blood pressure. When an increase in the circulating blood volume (excessive body fluid) is observed, dry weight should be initially decreased, and appropriate hypotensive therapy should be administered while confirming the effects.

Patients in whom hypertensive encephalopathy related to a rapid increase in blood pressure is

TABLE 14. *Side effects of recombinant human erythropoietin*

Side effects demonstrated in the literature at the high evidence level
Hypertension
Thrombosis/embolism
PRCA related to the appearance of an anti-EPO antibody
Other side effects reported
Convulsive attacks
Reduction of dialysis efficiency
An increase in residual blood/blood clotting in the extracorporeal circulation circuit
An increase in the anticoagulant requirement
Hyperpotassemia
Hyperphosphorusemia
Cold-like symptoms
Myleofibrosis
Visual hallucination

EPO, erythropoietin.

suspected have been reported; in particular, close follow-up and management are important in the phase in which the Hb (Ht) level is elevated immediately after the start of administration.

2. Thrombosis/embolism

The risk of thrombosis/embolism related to an increase in the Hb (Ht) level can not be ruled out.

In the follow-up involving a large-scale population, there was no increase in the risk of thrombosis/embolism related to administration of rHuEPO in Japan, excluding a case report in Okinawa (95). There have been a few case reports in which the relationship between thrombosis/embolism and administration of rHuEPO could not be ruled out. In other countries, it has been reported that administration of rHuEPO increases the risk of shunt (especially artificial blood vessel graft) occlusion; however, the risk increases when the Hb (Ht) value is normalized (96). In patients with ischemic heart disease or heart failure who are undergoing dialysis, it has been reported that the risk of mortality/non-fatal myocardial infarction increases when the Hb (Ht) value is normal (97). However, there are no medical grounds for the application of these results to general patients undergoing dialysis.

3. PRCA

An anti-EPO antibody induced PRCA in some patients.

Pure red cell aplasia is related to the appearance of an anti-EPO antibody (neutralizing antibody) (58). The details are introduced in the Administration method of rHuEPO (Chapter IV) and Resistance to EPO (Chapter V) sections. However, PRCA is a newly detected side-effect.

4. Others

Many concomitant symptoms/side-effects, such as convulsive attacks, reduction of dialysis efficiency, an increase in residual blood/blood clotting in the extracorporeal circulation circuit, an increase in the anticoagulant requirement, hyperpotassemia, hyperphosphorusemia, cold-like symptoms, myelofibrosis, and visual hallucination, have been reported. However, there is no association with rHuEPO, or currently, these side-effects are not considered significant.

CONCLUSION

It is our pleasure that we could prepare the guidelines for renal anemia in chronic hemodialysis patients in 2003/2004. The goal of chronic HD for improving renal anemia in Japan has been based on the guidelines prepared by the Science and Research Subsidy/Renal Failure Study Group, Ministry of Health and Welfare, in 1990. The target value of Ht (30%) differs from the values in other countries; it has been indicated that the target value in renal anemia treatment in Japan must be reviewed by scientific re-evaluation. Therefore, the JSDT established 'the Erythropoietin Working Group' (Chairman, Fumitake Gejyo), including two members specialized in hematology and medical statistics, in the Learning Committee, and this issue has been reviewed over about 3 years. During this period, several examination items to be solved have been raised. Initially, in a review of the scientific literature on the basis of evidence-based medicine (EBM), it was indicated that there were few high-grade scientific publications in Japan. Therefore, we aggressively reviewed the high-grade scientific literature in other countries, and re-analyzed the data on patients undergoing dialysis collected by the Statistical Survey Committee, JSDT, at a high collection rate in a retrospective study. As it has been indicated that hematological data depend on the timing/position of blood collection, we considered it necessary to clarify whether differences in the timing/position of examination between Japan and Europe/United States influence the examination results. Therefore, the Erythropoietin Working Group took countermeasures to confirm this, and employed the results as the reference data for reviewing the target value.

The results of the review showed that the Hb level at blood collection in the supine position, which is mainly performed in Japan, was lower than that at blood collection in the sitting position, which is mainly performed in Europe and the United States. In addition, the Hb level at blood collection 3 days after the day of previous dialysis, which is performed in Japan, was lower than that at blood collection 2 days after the day of previous dialysis, which is performed in Europe and the United States; an Hb level of 11–12 g/dL in Europe and the United States corresponded to that of 10–11 g/dL in Japan. Furthermore, the results of retrospective analysis in the JSDT survey on dialysis showed that there was no marked difference in the relative risk for mortality between the group with an Ht value of 30–33% and the group with an Ht value of 27–30%, whereas the relative risk was higher in the group with an Ht value of 33–36%. Based on the literature on the basis of EBM and the above results in Japan, we established the reference value of Hb in renal anemia treatment in Japan in 2004 as 10–11 g/dL (Ht: 30–33%). As there have been few high-grade scientific publications in Japan, some investigators doubted whether

the reference value was objectively determined. However, an Hb level markedly lower than that employed in Europe and the United States is applied as the reference value; considering the disadvantage for patients, we employed the above value as the reference value in 2004. In the future, when more scientific results are obtained in analysis of new studies/surveys, the guidelines for renal anemia treatment in 2004 will be replaced with new guidelines. Many members belonging to our society will inspect the guidelines for renal anemia treatment in 2004, and in the near future, more complete guidelines may be established based on new data evaluated as highly scientific.

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APPENDIX A

Records on committee meetings and intermediate report meetings held

First committee meeting, March 16, 2001
Second committee meeting, May 27, 2001
Third committee meeting, July 11, 2001
Fourth committee meeting, September 26, 2001
Fifth committee meeting, January 9, 2002
Sixth committee meeting, May 23, 2002
Seventh committee meeting, December 18, 2002
Eighth committee meeting, May 23, 2003
Ninth committee meeting, September 19, 2003
47th Congress of the JSDT, JSDT Consensus Conference, July 20, 2002, Tokyo, Japan
48th Congress of the JSDT, JSDT Twilight Session, June 20, 2003, Osaka, Japan

Abbreviations

AIDS: acquired immune deficiency syndrome
Alb: albumin
BUN: blood urea nitrogen
BW: body weight
CAPD: continuous ambulatory peritoneal dialysis
CI: confidence interval
Cr: creatinine
CRP: C reactive protein
EDTA: European Dialysis Transplantation Association
EPO: erythropoietin
Hb: hemoglobin
HD: hemodialysis
Ht: hematocrit
IL-6: interleukin-6
MCH: mean corpuscular hemoglobin
MCHC: mean corpuscular hemoglobin concentration
MCV: mean corpuscular volume
MHC: major histocompatibility complex
NKF-K/DOQI: National Kidney Foundation Kidney Disease Outcomes Quality Initiative
PRCA: pure red cell aplasia
PTH: parathyroid hormone
QOL: quality of life
RBC: red blood cell
rHuEPO: recombinant human erythropoietin
RR: relative risk
SD: standard deviation
SLE: systemic lupus erythematosus
TIBC: total iron binding capacity
TNF-α: tumor necrosis factor α
TP: total protein
TSAT: transferrin saturation
UIBC: unsaturated iron binding capacity
WBC: white blood cell