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2015 Japanese Society for Dialysis Therapy: Guidelines for Renal Anemia in Chronic Kidney Disease

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Abstract

Renal anemia is a complication of chronic kidney disease. Guidelines for safe and effective treatment in patients with renal anemia are needed. The Japanese Society for Dialysis Therapy (JSDT) published guidelines for the treatment of renal anemia in chronic hemodialysis patients in 2004 and in hemodialysis, peritoneal dialysis, predialysis, and pediatric patients in 2008. These two publications provide excellent guidance with respect to clinical practice issues, including the definition and diagnosis of renal anemia, the criteria for the initiation of treatment, target hemoglobin levels, iron supplementation therapy, blood transfusion, and side effects. The guidelines significantly improved the treatment of renal anemia in Japan. However, since 2008, many studies have assessed the treatment of renal anemia, and erythropoiesis-stimulating agents (ESAs) are now available. Therefore, the Executive Board of the JSDT decided that it was time to revise the guidelines to make them more appropriate to the situation of chronic kidney disease patients in Japan. This is the third edition of the guidelines for renal anemia published by the JSDT. The purpose is to improve the prognosis of chronic kidney disease patients, including after renal transplantation, through the treatment of renal anemia. The intended users of the guidelines are all healthcare professionals engaged in the treatment of chronic kidney disease. Regarding the treatment of adult dialysis and predialysis patients, statements and commentary are provided in the context of answers to clinical questions in Chapter 2 (Target Hb level and criteria for starting renal anemia treatment) and Chapter 4 (Evaluation of iron status and iron therapy). Furthermore, the essential information is provided alongside the critical issues in Chapter 1 (Diagnosis of renal anemia), Chapter 3 (Administration of ESAs—administration route and dose), Chapter 5 (ESA hyporesponsiveness), Chapter 6 (Side effects and concomitant symptoms of ESAs), and Chapter 7 (Red blood cell transfusion). In addition, the treatment of pediatric patients and post-renal transplant patients is discussed in Chapter 8 and Chapter 9, respectively.

Keywords: Guideline, Anemia, Chronic kidney disease, Erythropoietin-stimulating agents, Iron

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Scope

Background

Renal anemia is a complication of chronic kidney disease (CKD). The features of CKD are as follows: the frequency and severity of renal anemia increase with the progress of renal insufficiency, and the progress of anemia is accompanied by not only the deterioration in quality of life but also organ damage, such as deterioration of renal function or cardiac function due to chronic ischemia. Previously, the treatment of renal anemia relied on blood transfusion because no other effective treatment was available. In the 1980s, however, the treatment of renal anemia drastically changed with the development of recombinant human erythropoietin (rHuEPO). Since 1990, when it became possible to use rHuEPO in hemodialysis (HD) patients in Japan, therapeutic intervention has been promoted for renal anemia. Before this time, there were no guidelines for the management of renal anemia, and decisions regarding the timing, method, and target of therapeutic intervention were made according to trial and error. Guidelines for the safe and effective treatment for the majority of patients with renal anemia were therefore needed. In the late 1990s, various guidelines were prepared based on the clinical studies and statistical surveys accumulated in Europe and the USA. Since then, these guidelines have been revised or new guidelines have been published.

Preparation of guidelines

In Japan, the Japanese Society of Dialysis Therapy (JSDT) published the Guidelines for Renal Anemia in Chronic Hemodialysis Patients (Chairman, Fumitake Gejyo) for the first time in 2004. In 2008, the JSDT published the Guidelines for Renal Anemia in Chronic Kidney Disease (Chairman, Yoshiharu Tsubakihara), the target of which was expanded to include peritoneal dialysis (PD) patients, predialysis CKD patients, and pediatric patients. These two guidelines provided excellent information related to the issues of clinical practice, including the definition and diagnosis of renal anemia, the criteria for the initiation of treatment, target hemoglobin (Hb) level, iron supplementation therapy, blood transfusion, and side effects. The guidelines significantly improved the treatment of renal anemia in Japan. However, since 2008, there have been many studies on the treatment of renal anemia, rHuEPO has been markedly improved over the more than 30 years since its development, and erythropoiesis-stimulating agents (ESAs), including long-acting agents, have become available. Therefore, the need for new guidelines was discussed, and, in October 2012, the Executive Board and the Academic Committee of the JSDT decided that it was time to revise the guidelines so that they would be more appropriate to the situation of CKD patients in Japan. The Working Group (WG) on the Revision of Guidelines for Renal Anemia in Chronic Kidney Disease (hereafter, the third WG), whose aim was to prepare the revised third edition of the guidelines, was established in November 2012. Anemia in post-renal transplantation patients was included in these guidelines for the first time in Japan. The third WG started preparing guidelines for the treatment of renal anemia in all CKD patients, including HD patients, PD patients, predialysis CKD patients, pediatric patients, and post-renal transplantation patients.

Cooperation with related organizations in the preparation of the guidelines

The members of the third WG were selected not only from the JSDT. Those with expertise in the treatment of predialysis CKD patients, pediatric patients, and post-renal transplantation patients were invited from the Japanese Society of Nephrology, the Japanese Society for Pediatric Nephrology, and the Japanese Society for Clinical Renal Transplantation, respectively. Those with expertise in hematology and medical statistics were also invited to join the third WG.

Purpose of the guidelines

The purpose of the guidelines is to improve the prognosis of CKD patients in Japan through the treatment of renal anemia. The first issue discussed by the third WG was what information to include in the guidelines. This information should be reliable and useful in clinical practice. It was also important to clarify how to determine the grades of recommendation of the medical practices that seem to be most appropriate. In addition, the members agreed that the interpretation and evaluation of many lines of evidence accumulated to date are very important for preparing treatment guidelines suitable for CKD patients in Japan. Based on the above, the principles and procedures for the revision of the guidelines were established as described below.

Principles for the preparation of the guidelines

Targets The guidelines targeted all CKD patients, including HD patients, PD patients, predialysis CKD patients, pediatric patients, and post-renal transplantation patients. Post-renal transplantation patients were added as targets in the guidelines. The intended users of the guidelines are all healthcare professionals engaged in the treatment of CKD. Please note that the guidelines are designed for use in clinical practice and not as materials for medical lawsuits.

Style a) The most critical issues in the treatment of renal anemia were raised as clinical questions (CQs) and were discussed with respect to each type of patient.
b) Basic information was provided to complement the answers to CQs so that the guidelines could be more useful and easy to understand.

Literature search Research papers in the literature related to CQs and basic information written in English or Japanese and published in PubMed or Igaku Chuo Zasshi (ICHUSHI) during the period from 2003 to June 2014 were searched. Important research papers published before or after this period were manually searched and added to the target. The keywords for the literature search included anemia, kidney, renal, iron, overload, deficiency, and transplantation. Reports on animal experiments and genetic research were excluded from analysis.

Determination of statements and grades of recommendation Statements related to CQs and the grades of recommendation of the statements were discussed and determined in the plenary meeting of the WG. Care was taken to ensure that no bias was introduced while determining the target of analysis while collectively evaluating the relevant literature. If no consensus was reached, the CQs and grades of recommendation were adopted according to the agreement of more than two thirds of the members. When no CQs were raised but basic points alone were provided, the basic points were used not as statements but considered to represent the opinion of the WG with respect to the issue.

External review An External Review Committee was established independent of the third WG and was tasked to review the draft guidelines.

Literature evaluation

The following were some of the factors considered in the evaluation of reports in the literature selected as the target of analysis. It is usually expected that the contents of several guidelines are almost the same when those guidelines are prepared based on the same literature. However, when the context, ethnicity of subjects, and medical practices described in the literature vary, it is also important to determine whether the information is applicable to patients who are the targets of the guidelines being prepared. The differences in the background of the literature and the results were examined in the plenary meeting so that no bias was introduced into the evaluation of the literature. Part of the discussion at the plenary meeting was as follows. It is known that the life prognosis of HD patients in Japan is better than that in Europe and the USA. Although racial characteristics seem to contribute to this difference, it is also pointed out that this difference results from the differences in the dialysis therapy provided in Japan and abroad, including the purity of dialysate, the dialyzers used, and the arteriovenous fistula utilization rate. Such differences in medical conditions should be fully taken into consideration when interpreting various lines of evidence collected worldwide. Recently, there have been differences between evidence and clinical outcomes in Japan and other countries. The reasons for such differences were examined objectively after being discussed in the plenary meeting. Furthermore, although the JSDT's statistical surveys are classified as observational studies, the data collected by those surveys were regarded as direct evidence because they provided valuable information about a large number of HD patients in Japan. Although all of the treatments mentioned in the revised guidelines are assumed to be covered by health insurance in Japan, those treatments were not evaluated in terms of health economics.

Critical issues in clinical practice and CQs

Various issues arise, in daily clinical practice, with respect to treatment for renal anemia in Japan. However, if all such issues were considered critical in the guidelines, it would be difficult to distinguish which are the core principles for the treatment of renal anemia. Therefore, only the issues related to the following four items were considered as "critical" in clinical practice:

1) At which Hb level should the treatment of renal anemia be started?
2) What is the Hb level that should be maintained during the treatment of renal anemia?
3) Is it recommended to administer iron supplementation prior to ESA therapy?
4) What are the criteria for the initiation of iron supplementation therapy? Should there be any upper limits?

Specific CQs were raised focusing on these critical issues. Regarding the treatment of adult HD and PD patients and predialysis CKD patients, statements and commentary are provided in answers to the CQs in Chapter 2 (Target Hb level and criteria for starting renal anemia treatment) and Chapter 4 (Evaluation of iron status and iron therapy). Furthermore, the basic points that are essential to the safe and effective treatment of renal anemia are provided complementary to the

critical issues in Chapter 1 (Diagnosis of renal anemia), Chapter 3 (Administration of ESAs—administration route and dose), Chapter 5 (ESA hyporesponsiveness), Chapter 6 (Side effects and concomitant symptoms of ESAs), and Chapter 7 (Red blood cell transfusion). In addition, the treatment of pediatric patients and post-renal transplantation patients is discussed in Chapter 8 (Renal anemia in pediatric patients) and Chapter 9 (Post-transplant anemia in renal transplant recipients), considering the characteristics of the target patients. The style of description in these two chapters is similar to that in the chapters on the treatment of adult patients.

Indication and determination of statements and grades of recommendation

The answers to CQs were provided in the form of statements with grades of recommendation. The grades of recommendation were indicated by the combination of the strength of recommendation and the strength of evidence with reference to Minds2014. As described in the principles for the preparation of the guidelines, decisions were made by voting when no consensus was reached. Most of the statements were adopted unanimously. Only part of the statement regarding CQ3, "What are the criteria for starting and stopping iron therapy?" was adopted by the agreement of more than two thirds of all members. Because there was still room for discussion about this issue, an asterisk (*) was attached to this statement.

Strength of recommendation

1: **Recommend**
2: **Suggest**

*If a statement cannot be expressly recommended, it is indicated as "not graded."

Strength of evidence (examples)

A (Strong): High confidence in the estimate (e.g., meta-analyses)

B (Medium): Moderate confidence in the estimate (e.g., randomized controlled trials)

C (Weak): Limited confidence in the estimate (e.g., observational studies)

D (Very weak): Little confidence in the estimate (others)

The grades of recommendation in the revised version of the guidelines were determined by strictly following the procedure described above. However, because the procedure to determine the grade of recommendation was not exactly the same as that used in the 2008 version of the guidelines, there may be differences between the grades of recommendation of the statements indicated in the 2008 version of the guidelines and the revised version of the guidelines.

Process of preparation of guidelines

In accordance with the principles described above for the preparation of the guidelines, the third WG held 10 meetings, including ad hoc meetings, and drafted the revised version of the guidelines. We sincerely thank all committee members for their effort in collecting and comprehensively evaluating numerous research studies, exchanging opinions in earnest discussions, and drafting the guidelines despite their busy schedules.

External review

To increase the validity and transparency of the guidelines, an External Review Committee was established independent of the third WG and was requested to review the draft of the guidelines. The External Review Committee consisted of 22 members including Noritomo Itami (Chairman) and Takayuki Hamano (Vice Chairman), who were requested by the JSDT to fill these positions.

Review by the External Review Committee

The first meeting of the External Review Committee was held on January 15, 2014, and the committee spent 1 year reviewing the guidelines drafted by the third WG. The main points raised by the review were as follows:

1) The appropriateness of the established CQs and the principles of the preparation of the guidelines
2) The appropriateness of the number of research reports selected as the target of analysis
3) The appropriateness of the evaluation and interpretation of the literature
4) The appropriateness of the statements and commentary
5) The appropriateness of the grades of recommendation

The External Review Committee provided feedback four times to the third WG, which examined the feedback and modified the drafted guidelines. Although it was the first time that such a review process was adopted by the JSDT, the objective feedback provided by the External Review Committee was helpful for the preparation of the guidelines. We sincerely thank all members of the External Review Committee.

Final review by the Executive Board and Academic Committee of the JSDT

The Executive Board and the Academic Committee of the JSDT constituted the supervisory committee for the preparation of the guidelines and reviewed the drafted guidelines prepared by the process described above.

After the draft guidelines were approved by this committee, they were published on the website of the JSDT. Then, a public hearing was held and the draft guidelines were reviewed and modified based on the opinions expressed at the public hearing to establish the final version of the guidelines.

Promotion of the use of the guidelines in clinical practice

The following efforts aimed at improving the convenience for users and promoting the use of the guidelines:

- The guidelines were published on the website of the JSDT.
- Specific numerical values were provided (e.g., target Hb level).
- All medical treatments mentioned in the guidelines are covered by health insurance.

Future revision of the guidelines

The first and second editions of the guidelines for the treatment of renal anemia, were published by the JSDT in 2004 and 2008, respectively, and in 2015, the third edition was published. It will be important to review the treatment guidelines along with the development of novel drugs and the accumulation of new evidence.

Editorial independence

The total cost of preparing the guidelines was covered by the JSDT. No other organizations, institutions, or companies provided financial support.

Conflict of interest and securing of universality

1) All members of the third WG and the External Review Committee submitted a self-report on conflicts of interest to the Conflict of Interest Committee of the JSDT.
2) To ensure the absence of bias in the content of the guidelines, the members of the third WG were invited members not only of the JSDT but also of the Japanese Society of Nephrology, the Japanese Society for Pediatric Nephrology, and the Japanese Society for Clinical Renal Transplantation. Furthermore, those with expertise in hematology and medical statistics were invited in order to ensure the universality of the guidelines.

As described above, the Guidelines for Renal Anemia in Chronic Kidney Disease were revised using a new procedure for preparing evidence-based and reliable treatment guidelines. The utmost effort was made to make the guidelines as suitable as possible for the current state of renal anemia in Japan, although it was not easy to deal with all pathological conditions in CKD patients. We hope that the guidelines are helpful to healthcare professionals engaged in the treatment of patients with renal anemia with the aim of improving their prognoses.

December 2015

Hiroyasu Yamamoto, Chairman

Working Group on Revision of Guidelines for Renal Anemia in Chronic Kidney Disease

Guideline Preparation Committee

Japanese Society for Dialysis Therapy

Working Group on Revision of Guidelines for Renal Anemia in Chronic Kidney Disease

Chairman: Hiroyasu Yamamoto, Department of Internal Medicine, Atsugi City Hospital.

Vice Chairman: Shinichi Nishi, Division of Nephrology and Kidney Center, Kobe University Graduate School of Medicine.

Member and Chairman of Academic Committee: Tadashi Tomo, Blood Purification Center, Oita University Hospital.

Member and Chairman of Guideline Preparation Subcommittee: Ikuto Masakane, Department of Nephrology, Yabuki Hospital.

Member (Japanese Society for Clinical Renal Transplantation): Kazuhide Saito, Department of Urology, Niigata University Graduate School of Medical and Dental Sciences.

Member (Japanese Society of Nephrology): Masaomi Nangaku, Division of Nephrology and Endocrinology, The University of Tokyo.

Member (Japanese Society for Pediatric Nephrology): Motoshi Hattori, Department of Pediatric Nephrology, Tokyo Women's Medical University.

Member (invited): Takahiro Suzuki, Division of Hematology, Jichi Medical University (Present Address: Kitasato University School of Medicine).

Member (invited): Satoshi Morita, Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine.

Member: Akira Ashida, Department of Pediatrics, Osaka Medical College.

Member: Yasuhiko Ito, Department of Renal Replacement Therapy, Nagoya University Graduate School of Medicine.

Member: Takahiro Kuragano, Division of Nephrology and Dialysis, Department of Internal Medicine, Hyogo College of Medicine.

Member: Yasuhiro Komatsu, Division of Nephrology, Department of Medicine, St. Luke's International Hospital.

Member: Ken Sakai, Department of Nephrology, Toho University Faculty of Medicine.

Member: Yoshiharu Tsubakihara, Department of Comprehensive Kidney Disease Research, Osaka University Graduate School of Medicine (Present Address: Master Course of Management in Health Care Sciences, Graduate School of Health Care Sciences, Jikei Institute).

Member: Kazuhiko Tsuruya, Department of Integrated Therapy for Chronic Kidney Disease, Kyushu University Graduate School of Medical Sciences.

Member: Terumasa Hayashi, Department of Kidney Disease and Hypertension, Osaka General Medical Center.

Member: Hideki Hirakata, Division of Nephrology and Dialysis Center, Japanese Red Cross Fukuoka Hospital (Present Address: Fukuoka Renal Clinic).

Member: Hirokazu Honda, Division of Nephrology, Department of Medicine, Showa University Koto Toyosu Hospital.

(Japanese syllabary order; honorifics omitted)

Records of committee meetings and interim reporting

First meeting: November 30, 2012

Second meeting: April 18, 2013

Third meeting: June 14, 2013

Fourth meeting: November 24, 2013

Fifth meeting: January 17, 2014

Sixth meeting: April 18, 2014

Seventh meeting: May 16, 2014

Ad hoc meeting: June 13, 2014

Eighth meeting: July 3, 2014

Ninth meeting: August 15, 2015

Committee-sponsored symposium at the 58th Annual Meeting of the JSDT: June 21, 2013 (Fukuoka)

Committee-sponsored consensus conference at the 59th Annual Meeting of the JSDT: June 15, 2014 (Kobe)

Brief report on Guidelines for Renal Anemia at the 60th Annual Meeting of the JSDT: June 26, 2015 (Yokohama)

Draft guidelines approved by the Academic Committee of the JSDT: May 1, 2015

Draft guidelines published on the website of the JSDT: July 27, 2015

Public hearing on guidelines: August 15, 2015 (Tokyo)

Guidelines approved by the Executive Board of the JSDT: December 4, 2015

Summary of reviews by the External Review Committee

Background

The target hemoglobin (Hb) level suggested in the 2006 revised edition of the Kidney Disease Outcomes Quality Initiatives (KDOQI) anemia guidelines needed to be modified immediately after publication, when the results of the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trials were published 6 months later. Since then, there has been a growing emphasis on transparency, neutrality, and validity in the preparation of guidelines. If the statements are prepared by conducting a literature search aimed at finding answers to clinical questions (CQs) and by evaluating evidence, almost identical contents of the statements will be obtained. If there are differences between guidelines drafted by the Guideline Preparation Committee and the opinions of the External Review Committee under the same CQs, the examination of such differences will be helpful in enhancing the objectivity of the guidelines. This is why the External Review Committee was established.

Committee members

Among the nominated young researchers with an interest in renal anemia, Noritomo Itami, who was commissioned by the Japanese Society for Dialysis Therapy (JSDT) to serve as Chairman, selected 21 members who were specialists in internal medicine, pediatrics, and urology. He appointed Takayuki Hamano to serve as Vice Chairman. The members were approved by the Executive Board.

Methods

Because the Guideline Preparation Committee had achieved a consensus on the draft guidelines at the Annual Meeting of the JSDT in 2013, the External Review Committee followed the example of the Kidney Disease: Improving Global Outcomes (KDIGO) anemia guidelines published in 2012, on which comments were expressed by several countries.

With respect to the four CQs raised by the Guideline Preparation Committee, the External Review Committee searched and analyzed research papers that were written in English or Japanese and published in PubMed or Igaku Chuo Zasshi from 2003 to June 2014. The committee members were divided into five teams assigned to the themes of pediatric patients, renal transplantation, blood transfusion, target Hb level, and iron therapy, for conducting the literature search. They examined whether the statements correctly answered the CQs and assessed the strength of evidence for the statements by reviewing the relevant research papers. The strength of evidence was graded as follows, in a similar way as in the draft guidelines: A (strong; high confidence in the estimate), B (moderate; moderate confidence in the estimate), C (weak; limited confidence in the estimate), D (very weak; little confidence in the estimate), and not graded (a statement cannot be expressly recommended). There were a limited number of research papers from Japan that presented strong

evidence. However, the External Review Committee agreed with and followed the policy adopted by the Guideline Preparation Committee that the data collected from JSDT statistical surveys represent strong evidence, although those surveys were classified as observational studies. Moreover, at plenary meetings, the External Review Committee examined and confirmed whether the research papers were properly cited in the commentaries and whether the observations in such studies were accurately reflected in the commentaries. The results of the plenary meetings were reported to the Guideline Preparation Committee in the form of "Agreed" or "Modifications required" (with the reasons explained). In total, the External Review Committee re-examined the modifications of the draft guidelines shown by the Guideline Preparation Committee and provided feedback four times. The final draft of the guidelines was completed after six meetings of the External Review Committee.

Conclusions

In contrast to the evidence review team for the KDIGO guidelines, the External Review Committee did not conduct a thorough systematic review. However, the committee members of each team earnestly searched the literature and exchanged opinions at plenary meetings. Dr. Hamano is greatly appreciated for his leadership as the chairman of the meetings. The strength of evidence of 52 statements was evaluated as follows: 0 = A (strong), 3 = B (medium), 9 = C (weak), 8 = D (very weak), and 32 = not graded. There was no statement with the strength of evidence grade A, and grade B accounted for 5.7% of all statements. As the Chairman of the External Review Committee, Dr. Itami is responsible for all of the results and inadequacies of the assessment by the committee.

In the KDIGO guidelines, the strength of evidence was graded as A for 5.4% of all statements. It seems that the amount of strong evidence for the treatment of renal anemia is limited worldwide. The amount of data collected from JSDT statistical surveys and the number of reports on Japanese patients increased in the revised edition of the guidelines compared with those in the original version. In the future, it will still be necessary to accumulate more evidence on the treatment of renal anemia in Japan.

Finally, we hope that these guidelines will contribute to improvements in the prognosis of all patients with chronic kidney disease.

Noritomo Itami, Chairman of External Review Committee

Records of meetings of the External Review Committee

First meeting: January 25, 2014
Second meeting: April 12, 2014
Third meeting: May 24, 2014
Fourth meeting: August 10, 2014
Fifth meeting: November 1, 2014
Sixth meeting: January 25, 2015

External Review Committee

Chairman: Noritomo Itami, Kidney Center, Nikko Memorial Hospital (Present Address: Department of Nephrology, Itami Kidney Clinic).

Vice Chairman: Takayuki Hamano, Department of Comprehensive Kidney Disease Research, Osaka University Graduate School of Medicine.

Members:

Takaya Abe, Department of Urology, Iwate Medical University.

Hiroaki Ueda, Department of Pediatrics, Osaka City General Hospital.

Akira Okada, Division of Nephrology and Endocrinology, The University of Tokyo.

Tadashi Okada, Department of Nephrology, Hakuyu Chiyoda Clinic.

Daisuke Katagiri, Division of Nephrology and Endocrinology/Division of Hemodialysis and Apheresis, The University of Tokyo (Present Address: studying abroad).

Takayuki Katsuno, Department of Nephrology, Nagoya University Graduate School of Medicine.

Sawako Kato, Department of Nephrology, Nagoya University Graduate School of Medicine.

Noritaka Kawada, Department of Nephrology, Osaka Minato Central Hospital (Present Address: Osaka Bay Central Hospital).

Eiichiro Kanda, Department of Nephrology, Tokyo Kyosai Hospital.

Kan Kikuchi, Department of Nephrology, Shimoochiai Clinic.

Toshihiro Sawai, Department of Pediatrics, Shiga University of Medical Science.

Takaichi Suehiro, Department of Nephrology, Harasanshin Hospital (Present Address: Social Insurance Nakabaru Hospital).

Yuki Tsuruta, Department of Nephrology and Blood Purification, Tokyo Metropolitan Geriatric Hospital (at present: Department of Nephrology, Tsuruta Itabashi Clinic).

Hyogo Nakakura, Department of Pediatrics, Osaka Medical College (Present Address: Department of Hemodialysis and Apheresis, Arisawa General Hospital).

Toshihide Naganuma, Department of Urology, Osaka City University Medical School.

Masahiko Nagahama, Division of Nephrology, St. Luke's International Hospital.

Hiroki Nishiwaki, Division of Nephrology, Department of Medicine, Showa University Fujigaoka Hospital.

Kiichiro Fujisaki, Kidney Care Unit, Kyushu University Hospital.

Yukio Maruyama, Division of Kidney and Hypertension, the Jikei University Kashiwa Hospital (Present Address: Division of Kidney and Hypertension, the Jikei University Hospital).

Yukihiro Wada, Department of Nephrology, Department of Medicine, Showa University Hospital.

(Japanese syllabary order; honorifics omitted)

Information about conflicts of interest

In order for the WG members to maintain a neutral and fair perspective in the preparation of clinical practice guidelines, the JSDT makes every effort to avoid any conflict of interest that exists or that could arise in the future. All WG members are required to submit a signed document agreeing to disclose information about conflicts of interest that exist or could arise, and this form needs to be updated every year and modified whenever the situation changes. The submitted information is listed in the "Disclosure of conflicts of interest in the External Review Committee" below, and the records of the facts that support such information are kept by the Secretariat of the JSDT.

Reference

*)JSDT: JSDT Guideline on Conflict of Interest (COI) in Medical Research. 2011: http://www.jsdt.or.jp/jsdt/1370.html

Disclosure of conflicts of interest in the External Review Committee

Noritomo Itami: Received an honorarium for giving a lecture from Otsuka Pharmaceutical Co., Ltd. (a company that produces, sells, and imports/exports pharmaceuticals, clinical testing equipment, medical devices, and food products).

Sawako Kato: Received research grants from Sanwa Kagaku Kenkyusho Co., Ltd. (a company that conducts research and development, and produces and sells medical products and diagnostic agents), Kyowa Hakko Kirin Co., Ltd. (a company that produces and sells prescription drugs), Otsuka Pharmaceutical Co., Ltd. (a company that produces, sells, and imports/exports pharmaceuticals, clinical testing equipment, medical devices, and food products), and Sumitomo Dainippon Pharma Co., Ltd. (a company that produces and sells prescription drugs and diagnostic agents).

Kan Kikuchi: Received an honorarium for giving a lecture from Chugai Pharmaceutical Co., Ltd. (a company that produces, sells, and imports/exports prescription drugs) and Daiichi Sankyo Co., Ltd. (a company that conducts research and development, and produces and sells prescription drugs).

Toshihiro Sawai: Received travel expenses from Alexion Pharma (a company that produces, sells, and imports pharmaceuticals in Japan and abroad).

Hiroki Nishiwaki: Received research grants from Kyowa Hakko Kirin Co., Ltd. (a company that produces and sells prescription drugs).

Takayuki Hamano: Received an honorarium for giving a lecture and research grants from, and belongs to a project endowed by, Bayer Yakuhin, Ltd. (a company that develops, imports, produces, and sells pharmaceuticals, medical devices, and veterinary products), Kyowa Hakko Kirin Co., Ltd. (a company that produces and sells prescription drugs), Chugai Pharmaceutical Co., Ltd. (a company that produces, sells, and imports/exports prescription drugs), Glaxo-SmithKline K.K. (a company that conducts research and development and imports, produces, and sells prescription drugs and general pharmaceuticals), Furuno Electric Co., Ltd. (a company that produces, sells, and imports/exports medical instruments), Asahi Kasei Pharma Corporation (a company that produces and sells prescription drugs, diagnostic enzymes, diagnostic agents, and liquid food), Otsuka Pharmaceutical Co., Ltd. (a company that produces, sells, and imports/exports pharmaceuticals, clinical testing equipment, medical devices, and food products), and Baxter (a company that imports, produces, and sells dialysis products, plasma protein products, and drug administration systems).

(The members not listed above have no conflict of interest to report.)

Chapter 1. Diagnosis of renal anemia

1) Renal anemia occurs when the amount of erythropoietin (EPO) produced in the kidneys is insufficient to compensate for the decrease in hemoglobin (Hb) level. The diagnosis of renal anemia is made when chronic kidney disease (CKD) alone is the primary cause of anemia and there are no other diseases present that cause anemia. The measurement of serum EPO level is useful for the diagnosis of renal anemia in predialysis CKD patients.

2) The causes of anemia other than decreased EPO production capacity include the suppression of erythropoiesis, shortened red blood cell (RBC) survival time, disorders of iron metabolism, residual blood in the dialysis circuit, bleeding, and malnutrition due to various factors. These factors, however, are not yet fully understood.

3) Hb level should be used as a reference for the diagnosis of anemia. The following are appropriate reference Hb levels for the diagnosis of anemia in the Japanese population according to age and gender. These reference values are also used for the diagnosis of renal anemia. However, decisions regarding the treatment of renal anemia should be made based on the recommendations or suggestions in each chapter.

	< 60 years,	60-69 years,	≥ 70 years
Male:	Hb < 13.5 g/dL,	Hb < 12.0 g/dL,	Hb < 11.0 g/dL
Female:	Hb < 11.5 g/dL,	Hb < 10.5 g/dL,	Hb < 10.5 g/dL

4) In the diagnosis of renal anemia, it is necessary to differentiate renal anemia from various hematological diseases that can cause anemia. The following are useful criteria for differentiating blood diseases:
(1) Presence or absence of abnormalities of leukocytes and platelets (abnormalities in fractionation, morphology, and count, and the presence of myeloblasts)
(2) Cytometric categories by mean corpuscular volume (MCV) (microcytic, normocytic, and macrocytic)
(3) Increase and decrease in reticulocyte count
(4) Serum EPO level

Rationale

1) Renal anemia occurs when the amount of EPO produced in the kidneys is insufficient to compensate for the decrease in Hb level. The diagnosis of renal anemia is made when CKD alone is the primary cause of anemia and there are no other diseases present that can cause anemia. The measurement of serum EPO level is useful for the diagnosis of renal anemia in predialysis CKD patients.

EPO-producing cells in the kidneys are fibroblast-like cells in the peritubular interstitium of the proximal tubule that produce EPO in response to a low partial pressure of oxygen [1]. The partial pressure of oxygen surrounding EPO-producing cells is determined by the balance between the supply of oxygen from arteries and the oxygen consumption of tissues. The supply of oxygen is determined by renal blood flow and Hb level, whereas oxygen consumption is determined mainly by the Na re-absorption capacity of the proximal tubule [2].

In CKD patients, the supply of oxygen to tissues is suppressed due to decreased renal blood flow and, at the same time, local oxygen consumption decreases due to tubular defects. As a result, it is assumed that the partial pressure of oxygen surrounding the proximal tubule often remains within the normal range. In such cases, stimulation of EPO production capacity to compensate for the low partial pressure of oxygen is inappropriate. Therefore, when Hb level decreases for some reason, anemia persists because EPO production is not sufficiently induced. Renal anemia can be explained as anemia that becomes apparent when the amount of EPO produced in the kidneys is insufficient to compensate for the decrease in Hb level (relative deficiency).

There have been a number of reports on the relationship between Hb level and serum EPO levels. In these reports, most patients with hematopoietic disorders such as aplastic anemia and myelodysplastic syndromes (MDS) with Hb levels of <10 g/dL showed serum EPO levels of >50 mIU/mL [by radioimmunoassay or the chemiluminescent enzyme immunoassay (CLEIA)] [3, 4], whereas most CKD patients showed serum EPO levels of <50 mIU/mL [by enzyme-linked immunosorbent assay (ELISA) or the CLEIA method] [5, 6] (different measurement methods may affect the measured value of EPO, but such an effect has not been examined). Moreover, it has been reported that the increase in EPO level in response to the decrease in Hb level is suppressed at more advanced stages of CKD [6]. As a result, upregulation of EPO in response to the same degree of anemia is insufficient in CKD patients compared to those with normal renal function.

Serum EPO level is maintained within the reference range regardless of Hb level in most CKD patients [5, 6]. This finding indicates that EPO production is not sufficiently induced in CKD patients to reverse anemia. This suggests that, in addition to decreased EPO production capacity, there may be other factors contributing to the development of anemia in these cases. Some pathological conditions associated with CKD may be related to the development of anemia, but their details are not yet fully understood.

Rationale

2) The causes of anemia other than decreased EPO production capacity may be the suppression of erythropoiesis, shortened RBC survival time, disorders of iron metabolism, residual blood in the dialysis circuit, bleeding, and malnutrition due to various factors. These factors, however, are not yet fully understood.

It has been reported that various factors contribute to the development of anemia, in addition to the relative decrease in EPO production capacity in the kidneys, in CKD patients.

(1) Suppression of erythropoiesis

It has been pointed out that the levels of various uremic toxins are elevated in the blood of CKD patients and may suppress the formation of erythroblasts [7, 8]. However, the uremic toxins that suppress the formation of erythroblasts have not been identified, and their roles have not been sufficiently clarified. Because the levels of inflammatory cytokines such as interferon and tumor necrosis factor-α (TNF-α), which decrease the sensitivity of erythroblasts to EPO, increase in some CKD patients [9, 10], abnormal cytokine levels may be related to anemia in CKD patients.

(2) Shortened RBC survival time

It has been reported that RBC survival time is shortened by 30–60% in CKD patients, although the rate of shortening varies between reports. In a recent analysis using radioisotopes, the RBC survival time in hemodialysis (HD) patients was shortened by ~20% [11]. Osmotic fragility, RBC deformability, and RBC metabolism disorders due to red cell membrane dysfunction are considered to cause the shortening of RBC survival time, but the mechanisms are not yet fully understood.

(3) Disorders of iron metabolism

Serum hepcidin levels increase in CKD patients because of the enhanced synthesis of hepcidin in the liver, mediated by an inflammatory cytokine, interleukin-6, and due to the attenuated clearance of hepcidin in the kidneys [12]. Hepcidin is a peptide hormone that suppresses the release of iron from cells into the blood. The increase in hepcidin levels leads to decreased serum iron levels and increased intracellular iron levels (ferritin levels), causing defective iron utilization in the bone marrow and anemia (functional iron deficiency). It has been found that the increase in hepcidin level is a major cause of anemia associated with chronic inflammation and that a similar pathological condition is also observed in CKD patients.

(4) Residual blood in the dialysis circuit and bleeding

(5) Malnutrition

The risk of malnutrition is high in CKD patients, although the degree of malnutrition varies from patient to patient. The lack of nutrients required for erythropoiesis, such as vitamins and folic acid, can also accelerate the progression of anemia.

It is assumed that the above factors associated with CKD contribute to the decrease in Hb level and that the insufficient EPO production capacity in the kidneys leads to the persistence of anemia. However, which factors and to what extent they are really related to anemia have not yet been elucidated.

Rationale

3) Hb level should be used as a reference for the diagnosis of anemia. The following are the appropriate reference Hb levels for the diagnosis of anemia in the Japanese population according to age and gender. These reference values are also used for the diagnosis of renal anemia. However, decisions regarding the treatment of renal anemia should be made based on the recommendations or suggestions in each chapter.
<60 years, 60–69 years, ≥70 years
Male: Hb <13.5 g/dL, Hb <12.0 g/dL, Hb <11.0 g/dL
Female: Hb <11.5 g/dL, Hb <10.5 g/dL, Hb <10.5 g/dL

Because the physiological Hb level in healthy individuals varies according to age, gender, and race, the criteria for anemia diagnosis should be determined while considering these factors. It seems appropriate to use the mean − 2 standard deviations (SDs) of Hb level in Japanese individuals who were judged to be healthy by certain standards as reference values for the diagnosis of anemia. Table 1 shows the Hb levels in the Japanese population, and Table 2 shows the criteria for anemia diagnosis used in other countries. Target Hb levels and the criteria for starting treatment should be determined based on the recommendations or suggestions in the following chapters.

In blood tests using an automatic analyzer, which is now commonly used, RBC count, Hb level, and MCV are measurement values, and hematocrit (Ht) level is a calculated value. Unlike Hb level, which remains relatively constant after blood sampling, MCV changes due to various factors occurring with time after sampling and Ht level also changes with changes in MCV. Therefore, unless Ht level is measured directly, it is recommended to use Hb level as the criterion for anemia.

Rationale

4) In the diagnosis of renal anemia, it is necessary to differentiate renal anemia from various hematological diseases that can cause anemia. The following are useful for the differentiation of hematological diseases.
(1) Presence or absence of abnormalities of leukocytes and platelets (abnormalities in fractionation, morphology, and count, and the presence of myeloblasts)
(2) Cytometric categories by MCV (microcytic, normocytic, and macrocytic)
(3) Increase and decrease in reticulocyte count
(4) Serum EPO level

Table 1 Hemoglobin levels in the Japanese population by age and gender

	Miwa's Hematology 3rd edition [280]	Chronological Scientific [281]	
	19–60 years (g/dL)	60–69 years (g/dL)	70–79 years (g/dL)
Male (mean ± SD)	15.3 ± 0.9	13.8 ± 0.9	13.5 ± 1.2
Female (mean ± SD)	13.3 ± 0.9	12.5 ± 1.0	12.2 ± 0.9
Male (mean − 2SD)	13.5	12.0	11.1
Female (mean − 2SD)	11.5	10.5	10.4

Because there are various diseases that can cause anemia, it is important to differentiate renal anemia from anemia caused by hematological diseases. Figure 1 shows the differentiation chart.

In CKD patients with renal anemia, although EPO production is suppressed, EPO levels often remain within the reference range. Therefore, absolute EPO level is not a clear indication of decreased EPO production capacity, and it is necessary to compare EPO levels with Hb levels.

According to the re-analysis of data from Japanese clinical studies of recombinant human erythropoietin in predialysis CKD patients (conducted by Chugai Pharmaceutical Co., Ltd. and Kirin Pharma Co., Ltd.), the mean ± SD serum EPO level was 22.7 ± 12.1 mIU/mL (5.0–151.0 mIU/mL) and the mean + 2SDs serum EPO level was 46.9 mIU/mL [13] in 422 patients with a creatinine level of ≥2 mg/dL or a creatinine clearance rate of ≤30 mL/min and Hb level of <10 g/dL. Similar results were also obtained in studies abroad, although the EPO levels increased up to ~100 mIU/mL in some patients with stage 3 CKD [5, 6]. In contrast, EPO levels were >50 mIU/mL in most patients with hematological diseases [3, 4].

Considering the above, the measurement of EPO level is useful as an ancillary test in the diagnosis of renal anemia. If CKD patients show anemia (Hb levels <10 g/dL) and have EPO levels of <50 mIU/mL, they can be diagnosed with renal anemia. In contrast, when EPO levels are >50 mIU/mL, the EPO production capacity of the kidneys might be maintained and it may be necessary to consider the possibility of other diseases that can cause anemia. Particular attention is required for patients with EPO levels of >100 mIU/mL.

Reticulocyte count reflects the erythropoietic activity in the bone marrow. Reticulocyte count increases when the formation of erythroblasts is enhanced due to hemolysis or

Table 2 European Best Practice Guidelines and Kidney Disease Outcomes Quality Initiatives criteria for anemia

	EBPG [80] (g/dL)	KDOQI [282] (g/dL)
Adult male	Hb <13.5	Hb <13.5
Adult female	Hb <11.5	Hb <12.0
Male ≥70 years	Hb <12.5	

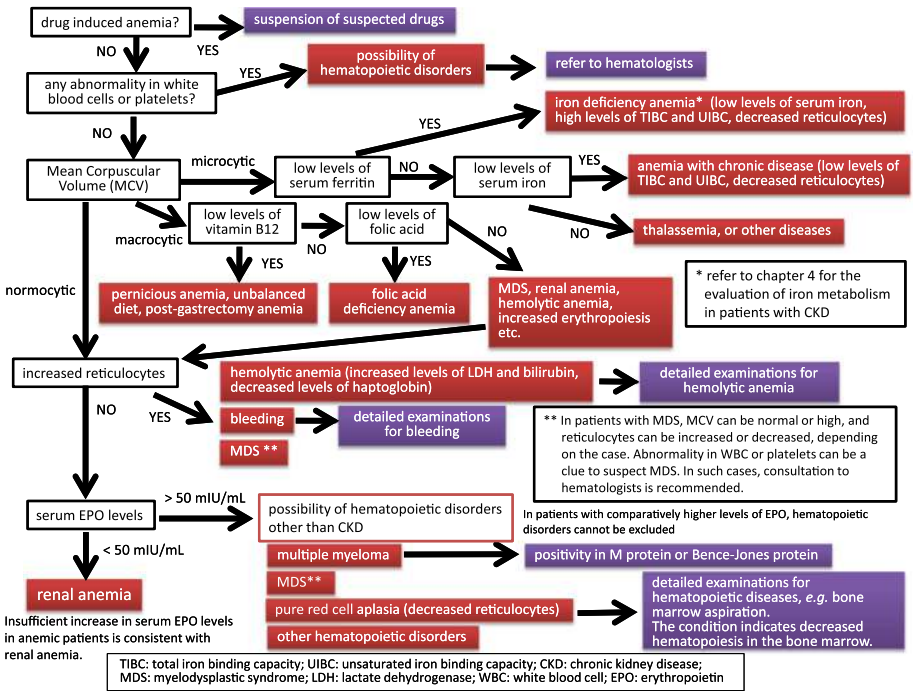

Fig. 1 An example of a diagnostic chart for anemic patients with chronic kidney disease

when patients are in the recovery phase after chemotherapy, but it remains within the normal range or decreases in patients with reduced erythropoiesis, including renal anemia. During the recovery of hematopoiesis, reticulocyte count increases in advance of the increase in Hb levels and is therefore useful as a pilot marker of the recovery of Hb levels.

When the recovery of hematopoiesis is observed after the administration of ESA, reticulocyte count typically increases in advance of the recovery of Hb levels. Therefore, reticulocyte count is useful as an indicator of ESA responsiveness. Usually, reticulocyte count increases within 1–2 weeks of the start of ESA administration, and then Hb levels increase. When the increase in reticulocyte count peaks, the increase in Hb level slows and the Hb level stabilizes. It seems appropriate to monitor the reticulocyte count at least once every 2 weeks after the start of ESA administration.

It is recommended to use the absolute value (RBC count × reticulocyte percentage) in the determination of reticulocyte count, but caution is required because the absolute value significantly varies depending on the RBC count. Therefore, it seems better to determine the increase and decrease in reticulocyte count based on both the absolute value and the reticulocyte percentage while considering the severity of anemia and the RBC count. However, during the recovery of erythropoiesis, reticulocyte production can be estimated by either the absolute value or the reticulocyte percentage because they both increase during this phase.

Although there is no established standard for the absolute value of reticulocyte count because the reference values vary among studies, a rough reference value is 50,000–100,000/μL when the RBC count is within the normal range.

Chapter 2. Target Hb level and criteria for starting renal anemia treatment

CQ 1: What are the target Hb levels to be maintained and the criteria for starting treatment in renal anemia?

Statement 1

1) In adult HD patients, we recommend that the target Hb levels to be maintained are in the range of 10–12 g/dL in the blood samples collected at the beginning of the week of HD. We recommend initiating the treatment of renal anemia when the Hb level is <10 g/dL in several test results. (1C)

2) In adult predialysis CKD patients, we suggest that the target Hb levels to be maintained are in the range of 11–13 g/dL. We suggest initiating the treatment of renal anemia when the Hb level is <11 g/dL in several test results. (2C) However, if the patient has a serious previous history of cardiovascular disease (CVD) or complications, or if it is medically necessary, dose reduction or the discontinuation of medication should be considered when the Hb level exceeds 12 g/dL. (not graded)

3) In adult peritoneal dialysis (PD) patients, we suggest that the target Hb levels to be maintained are in the range of 11–13 g/dL. We suggest starting the treatment of renal anemia when the Hb level is <11 g/dL in several test results. (2D) In the administration of ESA in PD patients, it is desirable to follow the guidelines for predialysis CKD patients. (not graded)

4) In the actual treatment of HD, PD, and predialysis CKD patients, we recommend to determine the target Hb levels according to the pathological conditions of individual patients by referring to the values provided above. (1C)

Rationale

Statement 1

In adult HD patients, we recommend that the target Hb levels to be maintained are in the range of 10–12 g/dL in the blood samples collected at the beginning of the week of HD. We recommend starting the treatment of renal anemia when the Hb level is <10 g/dL in several test results. (1C)

In the guidelines for the treatment of renal anemia published in 2004 [14] and 2008 [15], it was recommended that the treatment of renal anemia in HD patients should target Hb levels in the range of 10–11 g/dL in the blood samples collected in the supine position before HD at the beginning of the week (2 days after the last dialysis session).

The conventional lower limit of the target Hb level range, 10 g/dL, seems to be appropriate according to the results of observational studies conducted in Japan [16–19]. In the Japan Dialysis Outcomes and Practice Patterns Study (J-DOPPS), Akizawa et al. [17] reported the relationship between the Hb level at the start of observation and the risk of death in 5398 HD patients in Japan. They found that the risk of death in patients with Hb levels of <8 g/dL was significantly higher (by 78%) than that in patients with Hb levels in the range of 11–12 g/dL. There was a negative correlation between the risk of death and Hb level. Specifically, the risk of death decreased by 11%, as the Hb level increased by 1 g/dL.

Inaba et al. [18] reported that the risk of death in nondiabetic patients was highest in the group with Ht values of <27%. Furthermore, in the Japan Erythropoietin Treatment (JET) study, in which the survival prognosis in patients with different Hb levels was compared with that in the control group (patients with Hb levels of 10–11 g/dL), the survival rate was significantly lower in the group with Hb levels of <9 g/dL [19].

Hb levels have also been examined in terms of quality of life (QOL). In randomized controlled trials (RCTs), it was found that the vitality score [20], frequency of blood transfusion [21], and fatigue score [22] in the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) of QOL assessment were improved with the increase in Hb level. Although the results of some meta-analyses and the re-analysis of RCTs that have been recently published negate the idea that high Hb levels improve QOL [23–25], they suggested that QOL can be improved when Hb levels are increased up to 10 g/dL in patients with Hb levels <10 g/dL [23].

As mentioned above, in many previous observational studies, the risk of death was significantly higher in patients with Hb levels of <9 g/dL and tended to be higher in those with Hb levels of 9–10 g/dL than in those with Hb levels of 10–11 or 11–12 g/dL. It is also undesirable in terms of QOL that Hb levels remain <10 g/dL. Therefore, the recommended criteria for starting the treatment of renal anemia is when Hb levels are <10 g/dL in several test results.

As for the upper limit, Inaba et al. [18] classified patients into four groups by their Ht value (<27, 27–30, 30–33, and ≥33%) and reported that the survival rate increased with Ht. When the results were analyzed separately for diabetic and nondiabetic patients, there was no relationship between Ht level and survival prognosis in the diabetic patients. However, the risk of death was significantly lower in nondiabetic patients with Ht levels ≥33% than in those with Ht levels <27% [18]. In the JET study, while there was no significant difference in the risk of death between patients with Hb levels of 10–11 g/dL and those with Hb levels of 11–12 or >12 g/dL, the best result was obtained in patients with Hb levels of 11–12 g/dL, and the risk of death slightly increased in patients with Hb levels of >12 g/dL [19].

It has been established that high Hb levels decrease the frequency of blood transfusions and improve QOL in some patients [20–22]. In terms of survival and cardiovascular prognoses, there is little evidence supporting the recommended Hb levels of >12 g/dL. However, because there were no safety issues reported in the results of the JET study [19] or the clinical studies using darbepoetin alfa (DA) or continuous erythropoietin receptor activator (CERA) [26–28] at Hb levels of 10–13 g/dL, the recommended upper limit of the target Hb level range is 12 g/dL. In the 2008 version of the guidelines, the criterion for dose reduction and discontinuation of medication was defined as a Hb level of 12 g/dL, which is higher than the target Hb levels, and the range of Hb levels to be maintained during treatment was wider than that given in the 2004 version of the guidelines for the sake of easy management. As a result, the percentage of patients with Hb levels of <10 g/dL decreased from 34.7% at the end of 2008 to 27.0% at the end of 2012 [29]. A variation of approximately 1 g/dL is considered acceptable in daily clinical practice. In this revised version of the guidelines, the range of target Hb levels is widened to 2 g/dL on the basis of the results of observational studies conducted in Japan and considering ease of management.

As for the criteria for dose reduction and discontinuation of medication, the clinical studies conducted in Japan before 2008 [26–28] showed that there were no safety issues with high Hb levels within the range of 10–13 g/dL. In the JET study [19], however, the risk of death increased in patients with Hb levels of ≥12 g/dL, although there was no significant difference. Furthermore, RCTs in Europe and the USA [20, 30, 31] showed that Hb levels of >13 g/dL may lead to an increased risk of adverse events. The Hb level of 13 g/dL in Europe and the USA is considered to be not significantly different

from the Hb level of 12 g/dL in Japan in light of the data collected under the sampling conditions in Japan (in the supine position after an interval of 2 days after the last dialysis session), which differ from the sampling conditions in Europe and the USA [15]. Because the associated symptoms, dialysis conditions, and survival prognoses in HD patients in Europe and the USA largely differ from those in Japan, it is impossible to directly apply the results of clinical studies in Europe and the USA to guidelines for Japanese patients. However, until now, there has been no interventional study in HD patients in Japan. Some guidelines in other countries [32, 33] recommend not to intentionally increase Hb levels to ≥13 g/dL using ESAs. Therefore, taking account the difference in blood sampling conditions, this revised version of the guidelines recommends that dose reduction or discontinuation of medication should be considered when Hb levels exceed 12 g/dL. However, because the appropriate Hb level largely depends on the background features of individual patients, it should be determined for each patient considering the patient's EPO hyporesponsiveness [34, 35], history of cerebral stroke [36], presence of diabetes [18], presence of CVD [37], need for blood transfusion [21], and the effects of anemia on the patient's physical ability and QOL [22]. In addition, it should be noted that not only target Hb levels but also the rapid increase in Hb level [38] and the dose of ESA administered [39] may be related to morbidity.

Rationale

Statement 1

2) In adult predialysis CKD patients, we suggest that the target Hb levels to be maintained are in the range of 11–13 g/dL. We suggest starting the treatment of renal anemia when the Hb level is <11 g/dL in several test results. (2C) However, if the patient has a serious previous history of CVD or complications, or if it is medically necessary, dose reduction or the discontinuation of medication should be considered when the Hb level exceeds 12 g/dL. (not graded)

(1) Lower limit of the target Hb level range and criteria for starting treatment in predialysis CKD patients

When considering that the Hb level used as the criterion for starting ESA therapy in untreated patients with renal anemia is different from the target Hb levels to be reached by increasing or decreasing the ESA dose in patients who are already undergoing ESA therapy, it is possible to define the criterion for starting renal anemia treatment separately from the lower limit of the target Hb level range. However, in clinical practice, the administration of ESA is usually started according to target Hb levels, and the criterion for the initiation of ESA therapy is the lower limit of the target Hb level range, which will be described later. In a RCT conducted in the 1990s in which predialysis CKD patients who were treated with recombinant human erythropoietin (rHuEPO) were compared with those who were untreated, QOL was improved by increasing Ht values from 26.8 to 31.5% [40]. Furthermore, in a meta-analysis of predialysis CKD patients, QOL was improved by improvement in anemia in patients with Hb levels of 10–12 g/dL [41]. As will be described later, the results of the A21 study [42] conducted in Japan confirmed the renal protective effect of ESA targeting Hb levels of 11–13 g/dL. Considering these results, it seems appropriate that the treatment of renal anemia be started when the Hb level is <11 g/dL in several test results.

(2) Upper limit of the target Hb level range in predialysis CKD patients

The risk of cardiovascular events increased when target Hb levels were ≥13 g/dL. Therefore, it is recommended that target Hb levels be <13 g/dL instead and that the target Hb levels in individual patients be determined depending on their pathophysiological conditions, including subjective symptoms, cardiovascular complications, and decreased renal function.

Although some prospective clinical studies on predialysis CKD patients used cardiovascular protection as a primary endpoint, others used renal protection. The Guideline Revision Committee considered the possibility of discussing these endpoints separately, but concluded that it is not practical to set and recommend separate targets for cardiovascular protection and renal protection in clinical practice. Therefore, they defined the target Hb levels in predialysis CKD patients. Furthermore, when interpreting the results of clinical trials, the achieved Hb levels were emphasized in the assessment of endpoints, whereas the target Hb levels set to achieve the Hb levels in each clinical trial were emphasized in the determination of target Hb levels in this revised version of the guidelines. The upper limit of the target Hb level range was determined based on the results of a number of clinical trials in Europe and the USA, which reported increased cardiovascular events.

The studies reviewed in the revision of the guidelines were those that used hard endpoints and did not use surrogate markers such as left ventricular hypertrophy. At the time of preparing the 2008 JSDT Guideline for Renal Anemia in Chronic Kidney Disease, the CHOIR study [43] and the CREATE study [44] had been conducted as large-scale prospective clinical trials. The target Hb levels were set at 13.5 and 11.3 g/dL in the CHOIR study, and the results of intention-to-treat analysis showed that the incidence of primary endpoint events (a composite endpoint of death, myocardial infarction, hospitalization due to heart failure, and stroke) was significantly higher in the group with the target Hb level of 13.5 g/dL. However, a secondary analysis of the achieved Hb levels and rHuEPO doses in the

CHOIR study revealed that, among the patients randomly assigned to the high Hb level group, those who achieved higher Hb levels had better prognoses. The administration of high doses of rHuEPO was the factor that accounted for the poorer prognoses, and no relationship was observed between high target Hb level and poorer prognoses [45]. The target Hb levels were set at 13–15 and 10.5–11.5 g/dL in the CREATE study, and there was no significant difference between the high and low Hb level groups with respect to the incidence of cardiovascular events used as the primary endpoints (sudden death, myocardial infarction, acute heart failure, transient ischemic attack, hospitalization due to angina, peripheral arterial disease that required an amputation, and arrhythmia).

The significant studies carried out after the publication of the previous version of JSDT guidelines include the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study and the A21 study. In the TREAT study [36], which was a large-scale clinical study involving CKD patients with type 2 diabetes, the patients were divided into two groups: those who were administered DA with the target Hb level set at 13 g/dL, and those whose Hb levels fell below 9 g/dL but recovered to target levels. There was no significant difference between these two groups with respect to the incidence of cardiovascular events (death, myocardial infarction, heart failure, cerebral stroke, and hospitalization due to myocardial ischemia), which were used as the primary endpoints in this study. However, the incidence of stroke was higher, with a hazard ratio of 1.92 (95% confidence interval (CI), 1.38–2.68; $p < 0.001$), in the patients who were administered DA with the target Hb levels set at 13 g/dL. These results suggest that treatment targeted to achieve Hb levels of ≥13 g/dL cannot protect against cardiovascular events, but may rather increase the risk of adverse events. Taking into consideration the results of this study, the Evidence-Based Clinical Practice Guidelines for CKD 2013 published by the Japanese Society of Nephrology stated that "While some reports suggested that the treatment of renal anemia using ESA suppressed the progression of CKD and the onset of CVD, the therapy targeted to achieve Hb levels of >12–13 g/dL is less effective than that targeted to achieve Hb levels of 9–11.5 g/dL, but may rather increase the risk of onset of CVD (not graded)".

However, it should be noted that the incidence of cardiovascular events in Europe and the USA is higher than that in Japan. In the previous version of the guidelines, it was mentioned that the background features of the patients in the CHOIR and CREATE studies were largely different from those of common predialysis CKD patients in Japan because the frequency and severity of CVD in the patients in the CHOIR and CREATE studies were considerably higher than those in the HD patients reported in the preliminary results of a large-scale, prospective, observational study on the use of rHuEPO in Japan [46].

In the interim analysis of a survey on the specific use of DA in Japan, Darbepoetin Alfa for Renal Anemia Management in Japan (DREAM-J), the incidence of side effects during the observation period (mean = 1.2 years) was 5.3%. The incidence of side effects specifically affecting the cardiovascular system was 1.3% [47]. The results of multivariate Cox regression analysis with respect to the increase in the risk of cardiovascular adverse events did not indicate that the increased risk of cardiovascular adverse events was due to high Hb levels. A rate of increase in Hb levels >0.5 g/dL/week within 4 weeks of the start of DA administration was identified as a significant factor, but further discussion will be needed because the number of patients with a rate of increase >0.5 g/dL/week was small.

In the revision of the guidelines, the incidence of cardiovascular events and stroke was compared among the CHOIR and CREATE studies; the TREAT study, which was reported after the publication of the previous version of the guideline; the A21 study [42], which was an intervention study conducted in Japan; and the Gonryo study [48], which was an observational study conducted in Japan. As a result, the incidence of cardiovascular events was higher in Europe and the USA than in Japan. Furthermore, the incidence of stroke in Japan, which is well known to be high, was almost equal to or lower than that in Europe and the USA. However, it should be noted that there might have been bias because some cardiovascular events included in the TREAT and CHOIR studies were not included in the A21 and Gonryo studies, which may have resulted in the underestimation of the incidence of cardiovascular events in Japan (Table 3).

In the A21 study on Japanese predialysis CKD patients with serum creatinine (Cr) levels of 2.0–6.0 mg/dL, the patients were classified into the high Hb level group (target Hb levels of 11.0–13.0 g/dL, DA administration) and the low Hb level group (target Hb levels of 9.0–11.0 g/

Table 3 Incidence of cardiovascular events and stroke in clinical trials of erythropoiesis-stimulating agents

	Cardiovascular events (/1000 patients year)	Stroke (/1000 patients year)
CHOIR	51.7	5.4
CREATE	58	7.2
TREAT	76.4	9.5
A21	15.6	2.1
Gonryo (G3–5)	21.8	8.6

The events defined as cardiovascular events in each study were as follows: the events specified as primary endpoints in the CHOIR, CREATE, and TREAT studies; myocardial infarction, cerebral infarction, cerebellar infarction, lung congestion, and heart failure, which were specified as adverse events, in the A21 study; angina, myocardial infarction, heart failure, and stroke in stage G3–5 patients in the Gonryo study

dL, epoetin alfa administration). There was no significant difference in the incidence of adverse events between the two groups. The problem in the A21 study was that different types of ESA were used for the high Hb level and low Hb level groups, but there has been no report of differences in the type of ESA used affecting the incidence of adverse events. However, there is a possibility that the increased incidence of adverse events in the high Hb level group was a false-negative finding because the number of patients and the rate of patients with diabetes as a complication were relatively low, and the adverse events were subdivided in this study. Based on the discussion, the conclusion is as follows. It should be noted that some studies in Europe and the USA suggest that the risk cardiovascular events increases with higher target Hb levels (≥13 g/dL). However, the incidence of cardiovascular events in the studies conducted in Japan was lower compared with those reported in Europe and the USA, and there is little evidence in Japan that the incidence of cardiovascular events increases when the target Hb levels are 11–13 g/dL in patients without a risk of such events. Therefore, the target Hb levels of 11–13 g/dL for predialysis CKD patients provided in the previous version are adopted in this revised version of the guidelines. Furthermore, in accordance with the statement in the previous guidelines that "If the patient has a history of serious CVD or complications or if it is medically necessary, dose reduction or interruption should be considered if the Hb level exceeds 12 g/dL," we recommend that the target Hb levels be determined according to the pathological conditions of individual patients by referring to the values provided above. In particular, the presence of asymptomatic myocardial ischemia in HD patients is clinically important [49]. Sufficient care is also required for predialysis CKD patients who have asymptomatic myocardial ischemia.

(3) Target Hb levels to be maintained in predialysis CKD patients

The target Hb levels were examined with the aim of achieving renal protection without increasing the incidence of cardiovascular events.

Kuriyama et al. [50] reported that renal protection was achieved when Hb levels reached 11.8 g/dL in rHuEPO therapy. However, this result cannot be simply applied to current clinical practice because the control group in this study consisted of untreated patients with Hb levels of 8.3 g/dL.

In the CHOIR study, there was no significant difference between the high and low Hb level groups in terms of the number of patients requiring dialysis, which was set as a secondary endpoint [43]. In the CREATE study, there was no significant difference between the two groups with respect to the deterioration of estimated glomerular filtration rate (GFR) (which reflects renal function) that was set as a secondary endpoint, but the number of patients who required dialysis was significantly higher in the group with the target Hb level set at 13–15 g/dL [44]. In the TREAT study, there was no significant difference between the two groups in terms of the incidence of renal death, which was set as a secondary endpoint [36]. In the Anemia Correction in Diabetes (ACORD) study, which was conducted in CKD patients with diabetes at stages G1–G3, there was no significant difference in the rate of change of the estimated GFR, which was set as a secondary endpoint between a group with the target Hb level set at 13–15 g/dL and a group with the target Hb level set at 10.5–11.5 g/dL [51].

Gouva et al. divided nondiabetic CKD patients (age range, 18–85 years; Hb levels, 9.0–11.6 g/dL; serum Cr levels, 2–6 mg/dL) into the early intervention group (target Hb levels >13.0 g/dL) and the delayed intervention group (treatment started at Hb levels of <9 g/dL) and observed a significant improvement in the composite endpoint consisting of the doubling of Cr level, initiation of renal replacement therapy, and death, which was the primary endpoint of this study, in the early intervention group (target Hb levels, >13.0 g/dL) [52].

The A21 study in Japan was a multicenter, randomized, open-label, parallel-group study on predialysis CKD patients (Hb levels, <10.0 g/dL; serum Cr levels, 2.0–6.0 mg/dL). In this study, the patients received iron supplementation so that their transferrin saturation (TSAT) exceeded 20% and their serum ferritin levels exceeded 100 ng/mL. The results were compared between the high Hb level group (target Hb levels of 11.0–13.0 g/dL, DA administration) and the low Hb level group (target Hb levels of 9.0–11.0 g/dL, epoetin alfa administration) [42]. The primary endpoint was the length of time from the start of the study to the first occurrence of one of the following events: doubling of serum Cr level, initiation of maintenance dialysis, renal transplantation, or death. At the end of the study, the results were compared between the patients with Hb levels of 12.04 g/dL and those with Hb levels of 9.80 g/dL. Kaplan–Meier analysis showed no significant difference in the primary endpoint between the two groups. However, when the relative risk was calculated using the Cox proportional hazard model including age, gender, and baseline Cr level, the risk of the incidence of renal events was significantly lower (by 29%) in the high Hb level group than in the low Hb level group (95% CI, 0.52–0.98; $p = 0.035$).

Considering the results of the A21 study in Japan, it seems appropriate to set the target Hb levels at ≥11 and <13 g/dL in terms of renal protection; therefore, no change is made to the target Hb levels in predialysis CKD patients defined in the 2008 version of the guidelines. However, for patients with serious cardiovascular complications, or those at high risk of cardiovascular events, or if it is medically necessary in the opinion of the physician, it

is important to determine the target Hb levels in individual patients while considering safety issues (Table 4).

Caution is needed in the assessment of QOL because there are various items included, and they vary from study to study. In predialysis CKD patients, vitality, among other QOL items, will be particularly improved by increasing Hb levels sufficiently from baseline levels.

In a study of early correction of anemia, CKD patients with GFRs of 25–60 mL/min were divided into two groups, namely, those with the target Hb level set at 13–15 g/dL and those with the target Hb level set at 11–12 g/dL. This study was stopped at an early phase because of the risk of pure red cell aplasia (PRCA), but a significant improvement was observed in vitality in the assessment of QOL using SF-36 [53]. No significant difference was observed between the two groups in the assessment of QOL using SF-36 in the CHOIR study [43], but a significant improvement was observed in the assessment of QOL using SF-36 in the high Hb level group in the CREATE study [44]. In the TREAT study, the FACT-fatigue score was improved at all time points except at week 73, and improvements in energy and physical function were also observed in the assessment of QOL using SF-36 [54].

In the meta-analysis performed by Clement et al., physical function, general health, vitality, and mental health were improved in the high Hb level group [24]. In the analysis based on a systematic review conducted by Gandra et al. [41], general improvement in energy/vitality was observed in the assessment of QOL using SF-36. Although the difference in the achieved Hb levels (2.1 and 1.7 g/dL differences in the achieved Hb levels or 5.7% difference in Ht) between the two groups was large in the three studies that showed QOL improvements, the difference was small (1.3 and 0.5 g/dL differences in the achieved Hb levels) in the two studies that did not show QOL improvements. It seems that the difference in the achieved Hb levels between the two groups was reflected in the presence or absence of QOL improvements.

In the A21 study in Japan, a significant improvement in vitality was observed in the high Hb level group in the assessment of QOL using SF-36. This finding agreed with those of the studies conducted in Europe and the USA [55]. Therefore, vitality, among other QOL items, will be particularly improved by increasing Hb levels sufficiently from baseline levels.

Rationale

Statement 1

3) In adult PD patients, we suggest that the target Hb levels to be maintained are in the range of 11–13 g/dL. We suggest starting the treatment of renal anemia when the Hb level is <11 g/dL in several test results. (2D) In the administration of ESA in PD patients, it is desirable to follow the guidelines for predialysis CKD patients. (not graded)

(1) Basic policy of administration of ESA in PD patients

Currently, there are no guidelines in which anemia control in PD patients is discussed separately from that in predialysis CKD patients and HD patients. In JSDT and Kidney Disease: Improving Global Outcomes (KDIGO) 2012, anemia control in PD patients is discussed in association with that in predialysis CKD patients. In contrast, in the European Renal Best Practice position statement [56], PD patients are regarded as CKD-5D patients and are included in the discussion about HD patients. In the previous version of the guidelines, PD patients are regarded as similar to predialysis CKD patients. The reasons are as follows:

a) The pathological conditions of PD patients are very similar to those of predialysis CKD patients because, while hemoconcentration occurs due to fluid removal during HD, there is no such mechanism of hemoconcentration in PD.
b) The feature of PD is the maintenance of residual renal function in patients undergoing dialysis. Currently, the incremental PD method, in which PD is started using a small amount of dialysate and the dialysis dose is gradually increased with the decline of residual renal function, is used worldwide and in many dialysis facilities in Japan. According to the

Table 4 Clinical trials of erythropoiesis-stimulating agents in predialysis chronic kidney disease patients

	Number	%DM	High Hb level group			Low Hb level group		
			Baseline	Target	Achieved	Baseline	Target	Achieved
A21 2012	322	31	9.2	11–13	12	9.2	9–11	9.8
TREAT 2009	4038	100	10.5	13	12.5	10.4	>9 (rescue)	10.6
ACORD 2007	172	100	11.9	13–15	13.5	11.9	10.5–11.5	12.1
CREATE 2006	603	26	11.6	13–15	13.3	11.6	10.5–11.5	11.8
CHOIR 2006	1432	49	10.1	13.5	12.6	10.1	11.5	11.3
Gouva 2004	88	0	10.1	>13	12.9	10.1	>9	10.3
Kuriyama 1997	108		9.3	Treated	11.8	9	Untreated	8.3

2012 JSDT statistical survey, the amount of PD fluid used in the first year was <4 L/day in 15.6% of PD patients and <6 L/day in 39.8% of PD patients. According to the 2013 JSDT statistical survey, the urine output of patients who were undergoing PD for <1 year, for 1–2 years, and for 2–4 years was 916.9, 842.0, and 688.4 mL, respectively. These results indicate that dialysis therapy is performed as an extension of conservative therapy [57].

c) Because the evidence in PD patients alone is limited, it is necessary to discuss anemia control in PD patients, in association with that in predialysis CKD patients.

Taking hemoconcentration into consideration, PD patients who have started to undergo complementary dialysis should be treated in accordance with the guidelines for HD patients. Their Hb levels are assessed by blood sampling at the beginning of the week of HD.

(2) Target Hb levels to be maintained in PD patients

No prospective study or RCT has been clearly confined to the determination of target Hb levels in PD patients. In a retrospective study of 326 PD patients who were followed up for 15 years from 2003, the survival prognosis in patients with Hb levels of ≥12 g/dL was better than that in patients with Hb levels of <12 g/dL [58]. In a large-scale review of 13,974 PD patients conducted in 2004, diabetic and nondiabetic patients were divided into four groups according to their Hb levels. The results showed that the survival prognosis was better in patients with Hb levels of ≥11 g/dL, both in diabetic and nondiabetic patients [56]. In 2011, Molnar et al. conducted a study of 9269 PD patients and found that survival prognoses and cardiovascular prognoses were most favorable in the patients with Hb levels of 12–13 g/dL [59]. As discussed above, it is difficult to clearly define the target Hb levels in PD patients at this point because the evidence for the appropriate target Hb levels in PD patients is limited. Guidelines in other countries (KDIGO, UK, Caring for Australasians with Renal Impairment (CARI), and European Best Practice Guidelines (EBPG)) also do not define the target Hb levels for PD patients alone.

The use of DA and CERA, long-acting erythropoiesis-stimulating agents, was approved in 2007 and 2011, respectively, but the number of clinical trials of these two agents is also limited. There have been only two reports on the use of DA in PD patients in Japan, which were about switching to DA from other agents by intravenous and subcutaneous administration [60, 61]. There has been only one article published in Japanese reporting that CERA was safely used when the target Hb levels were set at 10–12 g/dL [62]. In other countries, there has been only one study of switching to CERA in PD patients [63]. Anemia in patients was well controlled after switching agents in all of these reports, indicating that there were no safety issues when the upper limit of the Hb level range was set at ≥12 and <13 g/dL (Table 5). However, it was pointed out that appropriate care and management are required in the treatment of patients with hypertension.

Since the publication of the CHOIR and CREATE studies in 2006 and the TREAT study in 2009 in predialysis CKD patients, there has been no study, neither in Japan nor globally, that has set target Hb levels at ≥13 g/dL. There have been few RCTs focusing solely on PD patients. Therefore, there is little evidence supporting the appropriateness of increasing Hb levels up to ≥13 g/dL. In addition, there have been no observational study involving target Hb levels of ≥13 g/dL in PD patients. Because PD patients should be treated according to the guidelines for predialysis CKD patients, it seems appropriate to adopt the conventional target Hb levels in predialysis CKD patients, ≥11 and <13 g/dL, as the target Hb levels in PD patients. Furthermore, it seems appropriate to consider dose reduction or discontinuation of medication when Hb levels exceed 13 g/dL.

The Hb level used as the criterion for initiation of treatment is the same as the lower limit of the target Hb level range; namely, treatment should be started "when the Hb level is <11 g/dL in several test results" as defined in the 2008 version of the guidelines. RCTs are needed to define the target Hb levels in PD patients in order to improve survival prognoses and reduce cardiovascular complications.

Chapter 3. Administration of ESAs—administration route and dose

1) For HD patients, ESAs should be intravenously administered through a dialysis circuit.

2) The dose and frequency of ESA administration should be determined by considering various factors, such as the type of ESA, the Hb level at the start of administration, the target Hb level, and the expected or target rate of improvement in anemia.

3) For predialysis CKD patients and PD patients, subcutaneous administration of ESAs is desirable. However, for patients who undergo PD/HD combination therapy, ESAs should be intravenously administered through a dialysis circuit, as recommended for HD patients.

Rationale

1) For HD patients, ESAs should be intravenously administered through a dialysis circuit.

2) The dose and frequency of ESA administration should be determined by considering various factors, such as the type of ESA, the Hb level at the start of administration, the target Hb level, and the expected or target rate of improvement in anemia.

Table 5 Clinical trials of long-acting erythropoiesis-stimulating agents in peritoneal dialysis patients in Japan

	Journal title	Number of patients	Length of study (weeks)	Target Hb levels (g/dL)	Hb levels at end of treatment (g/dL)	Serious adverse events	Other side effects (hypertension, etc.)
DA	Ther Apher Dial [63]	72	28	Target range: 11–12	New: 10.6	Death: 2 (unrelated)	Hypertension: 22
				Maintained: 10–13	Switched: 10.5		
DA	Clin Exp Nephrol [64]	96	28	11–13	11.9±1.2	Death: 0	Hypertension: 22
CERA	Jpn Pharmacol Ther [65]	63	48	10–12	SC: 10.88±0.70	Death: 0	Hypertension: 2
					IV: 10.78±0.93		
CERA	Ren Fail [66]	83	48	11–13	11.8±1.5	Death: 1 (unrelated)	Hypertension (not provided)

DA darbepoetin alfa, *CERA* continuous erythropoietin receptor activator, *SC* subcutaneous administration, *IV* intravenous administration

In Europe and the USA, many clinical studies comparing intravenous and subcutaneous injections revealed that subcutaneous injection of rHuEPO is more advantageous than intravenous injection in terms of the improvement in anemia and its long-lasting effect, as well as cost-effectiveness [64–77]. In the conventional European and US guidelines on therapy for renal anemia [78, 79], subcutaneous injection was also recommended for HD patients. However, from the point of view of the prevention of PRCA, the subsequent European and US guidelines stated that intravenous injection is more preferable for HD patients [80, 81], as similarly recommended later in the 2008 JSDT Guidelines [15]. In contrast, intravenous or subcutaneous injection was recommended for HD patients in the KDIGO guidelines published in 2012 [32].

However, intravenous injection of ESAs is recommended for HD patients because the advantages of subcutaneous injection versus intravenous injection of DA and CERA, which are newly developed drugs, are less significant compared with those associated with rHuEPO injection. One report showed that the serum half-life of intravenous DA is approximately three times that of rHuEPO [82]. Other reports showed that there is no significant difference in efficacy between intravenous DA and subcutaneous DA [83–85]. Another report showed that the efficacy of intravenous DA is higher than that of subcutaneous DA [86]. The serum half-life of CERA, whether intravenously or subcutaneously administered, is 4–6 days and approximately seven times that of rHuEPO. This is the longest serum half-life among ESAs. The serum half-life of intravenous CERA is almost the same as that of subcutaneous CERA.

The doses of ESAs used are as follows. According to the 2008 JSDT Guidelines, rHuEPO should be administered three times per week at an initial dose of 1500 U, which can be increased to 3000 U if anemia does not improve to the target level. DA should be administered once per week at a dose of 20 μg for HD patients who have not yet received rHuEPO, according to the drug package instructions. For patients who switch from rHuEPO to DA, the recommended dose of DA is once per week (15–60 μg) depending on the previous dose of rHuEPO. Reports show that a target Hb level can be maintained by administering DA once every 2 weeks [87, 88]. Therefore, DA can be administered once every 2 weeks in the dose range of 30–120 μg to maintain the Hb level. The dose of DA should be appropriately changed in accordance with several factors, including the severity of anemia and patient age. The maximum allowable dose is 180 μg per administration.

In December 2014, the use of DA was approved for patients with MDS. The approved dose is 240 μg once per week, which is much higher than that for patients with renal anemia. Because MDS patients are expected to have ESA hyporesponsiveness, the increased dose of DA is considered efficacious. However, the safety of high doses of DA for dialysis patients has not been confirmed. Therefore, therapy involving DA for dialysis patients with MDS should be planned in cooperation with hematologists.

CERA should be intravenously administered once every 2 weeks at an initial dose of 50 μg for HD patients who have not yet received rHuEPO according to the drug package inserts. For HD patients who switch from rHuEPO to CERA, CERA should be administered once every 4 weeks at an initial dose of 100 or 150 μg. It has also been reported that after anemia improves, CERA should be administered once every 4 weeks in the dose range of 25–250 μg to maintain the target Hb level. Reports show that the Hb level is maintained by administering CERA once every 2–4 weeks because of its long serum half-life [89–94]. However, the Maintenance of Haemoglobin Excels with IV Administration of CERA (MAXIMA) [90] and Patients Receiving CERA Once a Month for the Maintenance of Stable Hemoglobin (PROTOS) [91] studies, in which switching from rHuEPO to CERA in HD patients was examined in the form of RCTs, showed that an optimal Hb level, which is similar to the previous treatment with rHuEPO, was maintained by administering CERA once every 2 or 4 weeks but that the dose of CERA required to maintain an optimal Hb level once every 4 weeks was higher than that required once every 2 weeks. In Japan, Shimomura et al. examined 51 HD

patients who were administered CERA once every 2 weeks for 10 weeks then once every 4 weeks for 16 weeks [95]. They reported that the dose of CERA per week was increased 1.4-fold after the administration frequency was changed. The reasons for this were reported as follows: (1) it takes 6 weeks for the serum CERA level to stabilize, as shown by a Japanese clinical study [96], and (2) it takes approximately 12 weeks for the dose of CERA administered once every 4 weeks to stabilize after switching from rHuEPO [97]. Moreover, Toida et al. compared the efficacy of CERA administered once every 2 weeks after switching from rHuEPO with that of CERA administered once every 4 weeks after switching from rHuEPO in a RCT [98]. They reported that the Hb level decreased in patients who were administered CERA once every 4 weeks, while an optimal Hb level was maintained stably in those administered CERA once every 2 weeks. Thus, it was suggested that the administration of CERA once every 2 weeks is efficacious. In addition, a report showed that the serum hepcidin level in HD patients decreased 1 week after the administration of CERA but increased 2 weeks after administration, demonstrating the efficacy of CERA administered once every 2 weeks in terms of iron use [99]. As mentioned above, the administration of CERA once every 2 weeks may be more efficacious than that once every 4 weeks. In any case, the dose of CERA should be appropriately changed in accordance with several factors, including the severity of anemia and patient age. The maximum allowable dose is 250 μg per administration.

Rationale

3) For predialysis CKD patients and PD patients, subcutaneous administration of ESAs is desirable. However, for patients who undergo PD/HD combination therapy, ESAs should be intravenously administered through a dialysis circuit, as recommended for HD patients.

In the 2008 JSDT Guidelines, subcutaneous injection was recommended for ESA but intravenous injection was recommended for DA because DA products were only allowed to be administered intravenously at the time. In the 2015 JSDT guidelines, subcutaneous injection was suggested for all ESA products. International guidelines, such as the KDIGO 2012 Anemia Guidelines and the Canadian Society of Nephrology Anemia Guidelines 2008, also recommend subcutaneous injection for predialysis CKD patients and PD patients.

Previous DA products involved a large volume of fluid because of their shape and caused pain during subcutaneous injection. However, this problem has been addressed by recent developments [100]. A report showed that the half-life of subcutaneously injected DA tends to be longer than that of the intravenously injected form [88, 101]. Moreover, subcutaneous injection is also desirable to avoid damaging blood vessels, which can then be used for vascular access in future HD. If the patients require additional HD therapy, DA should be intravenously administered through a dialysis circuit, as recommended for HD patients.

Chapter 4. Evaluation of iron status and iron therapy

CQ2: What methods are recommended for evaluating iron status?

Statement 2

1) For CKD patients with anemia, iron status should be regularly evaluated to prevent iron deficiency or iron overload (once a month for patients on iron therapy, once every 3 months for patients not on iron therapy). (not graded)

2) Serum ferritin level and TSAT are recommended as iron indices. (1C)

CQ3: What are the criteria for the initiation and discontinuation of iron therapy?

Statement 3-1

1) For patients who are not treated with ESA or iron and cannot maintain target Hb levels, we suggest iron therapy prior to ESA therapy if the serum ferritin level is <50 ng/mL. (2D)

2) For patients who are treated with ESA and cannot maintain the target Hb level, we recommend iron therapy if the serum ferritin level is <100 ng/mL and TSAT is <20%. (1B)

Statement 3-2[*]

3) For patients who are treated with ESA and cannot maintain target Hb levels, we suggest iron therapy if both the following conditions are satisfied: (2C)
- Absence of disease that decreases iron utilization rate
- Serum ferritin level <100 ng/mL or TSAT <20%.

4) We do not recommend iron administration that targets the serum ferritin levels to rise to ≥300 ng/mL. (2D)

*This statement is the only statement that was accepted with the approval of two thirds (not all) of the members of the working group for preparing the guidelines. Further discussion is still required (refer to SCOPE).

CQ4: What methods are recommended for administering iron?

Statement 4

1) For predialysis CKD, HD, and PD patients, iron should be administered orally or intravenously. (2D)

2) Oral iron should be administered at 100 (105)–200 (210) mg per day while confirming the degree of iron storage. (not graded)

3) Intravenous iron should be slowly administered at 40–80 mg for predialysis CKD and PD patients when they visit hospitals and at 40 mg for HD patients at the end of a dialysis session once per week. (2D)

4) Intravenous iron should be administered by setting 13 administrations as one cycle while confirming the improvement in anemia and evaluating the iron status to ensure that the serum ferritin level is <300 ng/mL. (2D)

5) The re-administration of iron should be carefully determined after confirming iron status and the presence or absence of bleeding and hematological disease. (not graded)

Rationale

Statement 2

1) For CKD patients with anemia, the iron status should be regularly evaluated because patients may have iron deficiency or iron overload (once per month for patients on iron therapy, once every 3 months for patients not on iron therapy). (not graded)

In patients with absolute or functional iron deficiency, iron is insufficiently used for erythropoiesis. Among CKD patients with anemia, some have absolute iron deficiency and others are considered to have functional iron deficiency, which is caused by defective iron utilization in the bone marrow because of chronic inflammation despite sufficient iron stores. In addition, the administration of ESA might cause iron deficiency as a result of the use of iron for erythropoiesis.

One report showed that 48% of predialysis CKD patients with anemia who were not receiving ESA or iron had iron deficiency in the bone marrow, and 18% had iron overload [102]. Moreover, 60–70% of the patients with GFR levels <60 mL/min had serum ferritin levels <100 ng/mL and TSAT <20%, indicating the possibility that the number of patients with iron deficiency increases as CKD progresses [103]. HD patients might lose iron due to blood loss through the extracorporeal blood circuit or dialyzers and through blood sampling for tests [104, 105]. For the effective use of ESA, HD patients must be continuously provided with iron at the amount required to synthesize Hb and compensate for lost iron.

For predialysis CKD, HD, and PD patients, regardless of the use of ESA and iron, we recommend evaluating the iron stores regularly (once per month for patients on iron therapy, once every 3 months for patients not on iron therapy) on the basis of the serum ferritin level or other indices for the early detection of iron deficiency (not graded). Note that the serum ferritin level should be measured at least 1 week after the last administration of iron because the level temporarily increases after the administration of iron [106]. In addition, iron therapy for CKD patients should be discontinued when the target Hb level is maintained or the patient has adequate iron stores, because unintentional iron administration to CKD patients may cause iron overload.

If the serum ferritin level and TSAT do not increase and anemia is not improved despite the administration of more than a predetermined amount of iron, physicians should suspect blood loss or bone marrow failure and search for the source of blood loss or consider referral to a hematologist.

Statement 2

2) Serum ferritin level and TSAT are recommended as iron indices. (1C)

Currently, no diagnostic methods for iron deficiency or iron overload have been established. Liver and bone marrow biopsies for evaluating iron content are invasive and difficult to perform in the context of daily testing. Although various iron indices, such as serum ferritin level, TSAT, hemoglobin content of reticulocytes [107–111], percentage of hypochromic erythrocyte, erythrocyte zinc protoporphyrin [107, 112, 113], soluble transferring receptor [114, 115], and hepcidin [116] have been examined, their effectiveness in the evaluation of the iron status in CKD patients has not been established. In the 2015 JSDT guidelines, serum ferritin level and TSAT, which were previously used in the domestic and international guidelines regarding renal anemia, are recommended for use as iron indices, although these indices have limitations for diagnosing iron deficiency and iron overload.

Serum ferritin level is effective for determining iron deficiency. Patients with low serum ferritin levels should be diagnosed as having iron deficiency anemia. However, serum ferritin level varies in various disorders, such as inflammatory disorders, infections, hepatic disorders, and malignant tumors. Hence, defective iron utilization for erythropoiesis may be caused by the localization of iron even if serum ferritin level is normal or high [117]. Moreover, the methods for measuring ferritin levels have not been standardized, and baseline serum ferritin levels differ among measurement methods. Therefore, the values of serum ferritin level set in these guidelines should be used as references, rather than absolute values, to be examined alongside the baseline for each facility and the trend of the serum ferritin levels of individual patients [118]. TSAT also has various limitations as an iron index; for example, (1) both the numerator (Fe) and denominator (total iron binding capacity) are easily affected by factors other than iron status (e.g., inflammation, nutritional status) [119, 120], (2) the accuracy of diagnosis decreases for patients with lower TSAT because they are more easily affected by factors other than iron status (e.g., inflammation, nutritional status), and (3) TSAT shows a large circadian variation [121–124]. Therefore, TSAT should be used as an index for responsiveness to ESA rather than as an index of absolute iron deficiency.

Rationale

Statement 3-1

1) For patients who are not treated with ESA or iron and cannot maintain target Hb levels, we suggest iron therapy prior to ESA therapy if the serum ferritin level is <50 ng/mL. (2D)

A previous study reported that iron administration improves anemia, even among patients with high serum ferritin levels [125]. However, not all of the administered iron is effectively used for erythropoiesis and may

be accumulated in various tissues, resulting in iron overload [126–129]. Administering an excessive amount of iron not only can cause iron to accumulate in organs but can lead to the development of various complications such as cardiovascular [130–132] and infectious [133, 134] diseases.

The baseline serum ferritin levels for absolute iron deficiency in CKD patients have not yet been established. The guidelines on anemia provided by the British Society of Gastroenterology not only state that the baseline serum ferritin level for absolute iron deficiency is 12–15 ng/mL for patients without inflammation but also mention that patients with inflammation might have absolute iron deficiency even if the serum ferritin level is ≥50 ng/mL [135].

Patients with hyperferritinemia associated with inflammation should be excluded. It has been reported that CKD patients with larger iron stores and serum ferritin levels ≥100 ng/mL have a high risk of adverse events. A 2-year observation study of 1086 HD patients in Japan showed that those patients with ferritin levels persistently ≥100 ng/mL have an increased risk of cerebro- and cardiovascular complications and infectious diseases [136]. The initiation of iron therapy should be carefully considered because the long-term safety of iron supplementation in CKD patients is still unclear. Iron therapy prior to the start of ESA therapy is applicable only to patients with absolute iron deficiency, and we suggest that the baseline serum ferritin level should be set at <50 ng/mL.

Statement 3-1

2) For patients who are treated with ESA and cannot maintain the target Hb level, we recommend iron therapy if the serum ferritin level is <100 ng/mL and TSAT is <20%. (1B)

Administration of iron to patients receiving ESA improves anemia in terms of iron consumption by ESA and improvement in hyporesponsiveness to ESA. However, the number of studies on the criteria for iron therapy is small. Several studies mainly focused on improvements of responsiveness to ESA by iron administration and did not fully examine the long-term safety of iron administration.

The criteria for iron supplementation recommended in international guidelines greatly differ from those used in clinical practice in Japan. The 2012 KDIGO guidelines [137] recommend iron therapy for patients who are not treated with ESA or iron or who are treated only if an improvement in anemia or a decrease in ESA dose is desired, TSAT is <30%, and serum ferritin level is <500 ng/mL. Applying the same criteria for Japanese CKD patients may pose the risk of iron overload.

The 2008 JSDT Guidelines for Renal Anemia in Chronic Kidney Disease [15] specified TSAT ≤20% and serum ferritin level ≤100 ng/mL as the criteria for the initiation of iron therapy to minimize the risk of iron overload. In Japan, iron therapy is widely implemented based on the 2008 JSDT Guidelines. Better survival of patients with serum ferritin levels ≤100 ng/mL has been reported in multiple observational studies in Japan, which suggests the adequacy of the criteria [136, 138]. Therefore, these criteria for the initiation of iron therapy are also recommended in the 2015 JSDT guidelines.

Rationale

Statement 3-2[*]

3) For patients who are treated with ESA and cannot maintain target Hb levels, we suggest iron therapy if both the following conditions are satisfied: (2C)

- Absence of disease that decreases iron utilization rate

- Serum ferritin level <100 ng/mL or TSAT <20%.

According to the criteria in Statement 3-1, 2), patients with iron deficiency whose serum ferritin level exceeds 100 ng/mL because of inflammation or other reasons are excluded from iron therapy. In a study of 142,339 patients, stratified analysis was performed using the data of statistical surveys conducted by the JSDT to examine the ESA hyporesponsiveness and TSAT of dialysis patients on ESA therapy. The results showed that ESA hyporesponsiveness increased with decreasing TSAT [139]. The Hb level decreases for patients with TSAT <20% regardless of the serum ferritin level (whether ≥100 or <100 ng/mL), and the ESA index (ESAI) remains high for TSAT up to 30–40%. This finding suggests that iron therapy may improve anemia or reduce the ESA dose for patients with moderately high serum ferritin levels (≥100 ng/mL) if TSAT is <20%. Moreover, 36% of dialysis patients in Japan have serum ferritin levels of <50 ng/mL and 58% have serum ferritin levels of <100 ng/mL. With this in mind, in the 2015 JSDT guidelines, we suggest iron therapy for patients who are receiving ESA and cannot maintain the target Hb level if the serum ferritin level is <100 ng/mL or TSAT is <20% and patients without dysutilization of iron for erythropoiesis.

We added the condition of "absence of disease that decreases iron utilization rate" because of the following. Elevated serum ferritin levels observed in some patients with TSAT <20% may reflect diseases such as inflammation or malignant tumors, and may not represent total body iron stores. Because such patients have a dysutilization of iron for erythropoiesis, iron overload may be induced by inappropriate iron supplementation. Therefore, physicians should fully examine the clinical conditions of patients before the initiation of iron therapy and carefully determine the applicability of iron administration to these patients.

Statement 3-2[*]

4) We do not recommend iron administration that targets the serum ferritin levels to rise to ≥300 ng/mL. (2D)

Iron level is strictly controlled in living bodies because iron is toxic when excessively present. CKD patients are frequently subjected to intravenous iron administration and transfusion and have a risk of iron overload because there is no excretion pathway for the iron once intravenously administered. Although the possibility that iron overload increases the risk of infectious disease and cardiovascular events has been raised, the cutoff serum ferritin level as a diagnostic criterion for iron overload has not been determined. Moreover, the effects of iron overload on the QOL and survival of CKD patients are unclear, requiring further studies.

The number of studies on the association between iron overload and the survival and adverse events of predialysis CKD patients is small. A study examining predialysis CKD patients has revealed that high TSAT is associated with a decrease in GFR and that the mortality rate tends to increase in patients with advanced CKD with serum ferritin levels ≥250 ng/mL [140].

The possibility that excessive intravenous administration of iron in HD patients increases the risk of cardiovascular events has been reported previously: Kuo et al. [132] classified patients into four groups: non-administration group and 6-month iron administration groups with doses of 40–800 mg (group I), 840–1600 mg (group II), and 1640–2400 mg (group III). The authors reported that although there was no significant difference in the risk of CVD between the non-iron administration group and group I, patients in group II and group III were at significantly higher risks for cardiovascular events compared with patients in the non-iron administration group. Brookhart et al. [134] also reported that the group with high-dose intravenous iron administration (≥600 mg within 30 days) showed a higher risk of hospitalization associated with infectious disease compared with patients treated with low doses of intravenous iron.

Moreover, the relationships among liver iron content, serum ferritin level, and iron dose in HD patients were analyzed using a superconducting quantum interference device (SQUID) [126] and magnetic resonance imaging (MRI) [127–129]. The study using the SQUID [126] showed that iron was accumulated in the liver of patients with serum ferritin levels ≥340 ng/mL. The study using MRI revealed that iron was accumulated in the liver of 84% of patients who received intravenous iron and that the cutoff serum ferritin level was 290 ng/mL in patients with severe iron accumulation [129].

Iron administration deteriorates phagocytic function in gram-positive and gram-negative bacteria and induces apoptosis in polymorphonuclear neutrophil leukocytes [141]. Iron is also necessary for the proliferation of bacteria [142], and for this reason, the possibility of an association between iron administration and the proliferation of bacteria has been raised [143]. Although one study found no significant association between high serum ferritin levels and the incidence of infections [144], other studies have shown that the risk of infections and the incidence of sepsis and vascular access-related infections significantly increased in HD patients with serum ferritin levels >331 and >500 ng/mL [145–147]. A systematic review of the safety and efficacy of intravenous iron showed that intravenous iron administration was effective for improving anemia and avoiding transfusion but that it caused a significantly higher risk of infectious disease [133].

A national survey in Japan, which was conducted by the JSDT in 2012, analyzed the relationship between ESA hyporesponsiveness and serum ferritin level in maintenance HD patients. This survey revealed that ESAI tended to increase at serum ferritin levels ≥300 ng/mL, suggesting the possibility that the responsiveness to ESA in patients with serum ferritin levels ≥300 ng/mL is not necessarily improved by iron administration. Currently, the upper limit of serum ferritin level used to predict the prognosis of CKD patients has not been clearly determined, and the long-term safety of iron therapy for CKD patients is unclear. To minimize the risk of iron overload, iron supplementation to maintain a high serum ferritin level should be avoided for safety reasons in CKD patients. Considering that patients with serum ferritin levels ≥300 ng/mL account for only 10% of the dialysis patient population in Japan, we do not recommend iron administration that targets the serum ferritin level to rise to ≥300 ng/mL.

Rationale

Statement 4

1) For predialysis CKD, HD, and PD patients, iron should be administered orally or intravenously. (2D)

2) Oral iron should be administered at 100 (105)–200 (210) mg per day while confirming the degree of iron storage. (not graded)

3) Intravenous iron should be slowly administered at 40–80 mg for predialysis CKD and PD patients when they visit hospitals and at 40 mg for HD patients at the end of a dialysis session once per week. (2D)

4) Intravenous iron should be administered by setting 13 administrations as one cycle while confirming the improvement in anemia and evaluating the iron status to ensure that the serum ferritin level is <300 ng/mL. (2D)

5) The re-administration of iron should be carefully determined after confirming iron status and the presence or absence of bleeding and hematological disease. (not graded)

In Japan, oral and intravenous administration of iron is approved for CKD patients. Sodium ferrous citrate, ferrous fumarate, and iron sulfate hydrate are available forms of oral iron. In addition, some oral phosphate binders

contain iron and have been reported to increase serum ferritin level when administered to patients with CKD. Physicians need to be careful to avoid iron overload when prescribing these agents.

Oral iron therapy has some problems, such as the deterioration of absorption, low compatibility with other agents, and digestive symptoms including nausea and vomiting [148]. Moreover, an association between oral iron administration and the risk of colorectal cancer has been reported [149]. Intravenous iron therapy is superior to oral iron therapy in terms of medication adherence and fewer digestive symptoms; however, some patients wish to avoid intravenous iron administration in order to reserve the vein for vascular access in future dialysis treatment. Hence, patients may develop iron overload if intravenous iron administration is unintentionally continued. An association between acute reactions and intravenous iron has been reported, although not frequently. Moreover, a systematic review of iron therapy showed that the risk of infectious disease in patients treated with intravenous iron was significantly higher than that in patients treated with oral iron [133]. Most previous studies comparing the efficacy of intravenous iron and oral iron focused on the ESA dose and anemia improvement, and few studies compared the long-term safety of both options in terms of QOL and survival. Oral or intravenous iron therapy should be selected by comprehensively examining the conditions and the degree of need for iron supplementation of individual patients.

(1) Administration route of iron for predialysis CKD and PD patients

A RCT study in 96 predialysis CKD patients showed that oral iron administration significantly increased Hb level without increasing serum ferritin level and that there was no significant difference in the improvement in anemia between oral iron and intravenous iron administration [150]. A systematic review examining the available iron administration methods for predialysis CKD patients [151] showed that there was no difference in the improvement in anemia between oral iron and intravenous iron in two of the seven RCT studies, whereas oral iron administration improved anemia more effectively than intravenous iron in the remaining studies. Unlike HD patients, predialysis CKD patients have difficulty in securing the intravenous administration route, and the veins should be reserved for vascular access for future dialysis treatment. Therefore, oral iron therapy should be adopted for predialysis CKD patients, and intravenous iron therapy should be considered if oral administration is difficult because of digestive symptoms or if the patient cannot maintain the target Hb level with oral iron alone. The same principle should be applied for PD patients.

(2) Administration route of iron for HD patients

Currently, many HD patients are treated with intravenous iron because of easy access to the administration route and poor iron absorption by the digestive tract. However, intravenous iron therapy should not necessarily be selected as a first choice, and oral iron is a viable option for HD patients. Therefore, the administration route of iron for HD patients should be selected depending on the conditions of individual patients.

Some studies of HD and PD patients showed that intravenous iron was more effective for improving anemia and reducing the ESA dose than oral iron [125, 142, 152–156]. However, these studies do not deny the efficacy of oral iron. In all of the studies, oral iron significantly improved anemia in HD patients, particularly in those patients with smaller iron stores. One report showed that there was no significant difference in the percentage of patients achieving the target Hb level (11–12 g/dL) between HD patients receiving oral iron and those receiving intravenous iron [157]. Another report showed that at least 73% of HD patients receiving oral iron maintained Hb levels ≥11 g/dL and at least 93% maintained Hb levels ≥10 g/dL, confirming that oral iron is effective for improving anemia in HD patients [158].

Hepcidin plays a key role in the regulation of the utilization of iron for erythropoiesis and the absorption of iron through the gastrointestinal tract [159]. In iron overload, the expression of hepcidin in the liver increases and degrades divalent metal transporter 1, which regulates the absorption of iron in the duodenal epithelia [160] and inhibits the absorption of iron through the gastrointestinal tract. In iron deficiency, the expression of hepcidin in the liver decreases and the absorption of iron from the gastrointestinal tract increases. It has been suggested that the serum hepcidin levels of CKD patients are higher compared with those of healthy individuals. However, a recent study revealed that the serum hepcidin levels of all HD patients were not necessarily significantly higher compared with those of healthy individuals and that the serum hepcidin levels in 46% of HD patients were within the healthy range [161]. Thus, it is possible that in HD patients with small liver iron stores, the hepcidin level is low and the absorption of iron through the digestive tract may not be inhibited. In addition, it has been pointed out that hepcidin may be suppressed by long-acting ESAs [162]. To avoid iron overload, oral iron therapy can be an effective choice in HD patients as well as in predialysis CKD and PD patients.

(3) Methods for administering iron

If patients satisfy the criteria for the initiation of iron therapy, as mentioned above, and have no contraindications

for iron [see (4)], oral iron should be administered at 100 (105*)–200 (210*) mg per day (*amount of iron in iron sulfate hydrate). If iron deficiency does not improve or the Hb level does not improve without iron overload, intravenous iron administration is recommended.

It is possible that unintentionally administering oral iron causes patients to develop iron overload. Therefore, physicians should consider reducing the dose of oral iron or discontinue the therapy when the patients reach the target Hb level. In intravenous iron therapy, 40–80 mg of saccharated iron oxide (1A, 2 mL, 40 mg iron) should be slowly administered to predialysis CKD and PD patients when they visit hospitals, and 40 mg should be slowly administered to HD patients via the extracorporeal blood circuit at the end of a dialysis session once every 1 or 2 weeks. One cycle of intravenous iron therapy should consist of 13 administrations, during which the improvement in anemia and iron status should be evaluated. When serum ferritin level is ≥50 ng/mL and the target Hb level is maintained, intravenous iron therapy should be re-examined so that the serum ferritin level is kept <300 ng/mL. In the 2008 JSDT Guidelines for Renal Anemia in Chronic Kidney Disease [15], the maximum number of iron administrations, calculated from the total amount of deficient Hb iron and iron loss, is set at 13, after which the re-examination of iron therapy is recommended. Although this is not based on robust evidence, in the 2015 JSDT guidelines, iron therapy should also be re-examined by setting 13 administrations as one cycle to ensure safety and prevent unintentional administration.

Administering a high dose of intravenous iron over a short period has advantages, such as a high rate of increase in the Hb level and a high rate of reduction in the ESA dose. In contrast, high doses of iron administered rapidly are not necessarily effective for erythropoiesis and may be accumulated in various organs, including reticuloendothelial tissues. Low-dose intravenous iron therapy has advantages, such as the prevention of iron overload, maintenance of stable iron stores, effective utilization of administered iron for erythropoiesis [163], and suppression of variability of Hb level [164]. It has been reported that HD patients who are treated with intravenous iron at 50 mg/week for 6 months maintained the target Hb levels with increasing ESA doses [165]. In contrast, another report showed that even low-dose (31.25 mg/week) intravenous iron for 12 months increased serum ferritin levels to 380 ng/mL [166], suggesting that the risk of iron overload should always be taken into account. Currently, few clinical studies have compared the improvement in anemia, adverse events, and survival between patients treated with high-dose intravenous iron administration over a short period and patients treated with low-dose intravenous iron. An observational study of 58,058 maintenance dialysis patients showed that the all-cause mortality rate and risk of cardiovascular death increased when the intravenous iron dose exceeded 400 mg/month but decreased at doses up to 399 mg/month [167]. This result indicates that appropriate iron therapy may decrease the risk of death.

A recent study comparing 776,203 HD patients with iron doses <200 and ≥200 mg/month showed that the risks of infection-related hospitalization and death increased in patients receiving an intravenous iron dose ≥200 mg/month [134]. In addition, a 2-year observational study of 1086 HD patients in Japan showed that the risks of cardio- and cerebrovascular complications and infections significantly increased in patients receiving an intravenous iron dose ≥50 mg/week compared with patients not on iron therapy [136]. Considering these findings, intravenous iron doses ≤50 mg/week and <200 mg/month are desirable in terms of safety. In summary, intravenous iron should be administered once per week by setting 13 administrations as one cycle while confirming its efficacy in terms of improvement in anemia and evaluating iron status to ensure that the serum ferritin level is <300 ng/mL and the risk of iron overload is minimized.

Acute reactions (e.g., pulse abnormalities, blood pressure reduction, breathing difficulties) manifesting when intravenous iron is administered have also been reported, although their frequencies were unclear. Physicians should be familiarized with the potential risks and notes described in the package inserts of intravenous iron, assume the manifestation of acute reactions, and prepare a possible response system before administering iron. They should carefully observe the patients during and after iron therapy. If the patients display shock/acute reactions, a feeling of discomfort, chest distress, and nausea or vomiting, physicians should stop the therapy and prescribe appropriate alternative treatment. The iron status of patients should be regularly evaluated during and after iron therapy. For predialysis CKD patients and PD patients with residual renal function, the trend of their renal function should also be evaluated.

(4) Contraindication, careful administration, and notes for iron therapy

There are contraindications and precautions for iron therapy, and caution should be exercised before initiating iron therapy even if patients meet the criteria for starting treatment. Physicians should carefully examine if iron therapy is appropriate for each patient, even if they have iron deficiency.

[1] In the following cases, iron therapy should be stopped:

(1) Hypersensitivity to iron agents or additives, such as a history of anaphylaxis caused by iron therapy.

(2) A history of diseases or symptoms that might be caused by iron overload, massive transfusion, hemosiderosis, or iron-related osteomalacia, among others.
(3) Severe hepatic disorders.

[2] In the following cases, iron therapy should be carefully determined considering the benefits and risks of iron administration:

(1) Paroxysmal nocturnal hemoglobinuria: this may induce hemolysis.
(2) The presence of infections: these have been reported to cause complications, such as bacterial infections and mycoses, or exacerbate these infectious diseases when iron is administered.
(3) Viral hepatitis: the 2011 JSDT Guidelines for the Treatment of Hepatitis C Virus (HCV) Infection in Dialysis Patients [168] gave the following recommendation: iron inhibits the activity of hepatic cells and exacerbates chronic hepatitis C when excessively accumulated in the liver. Considering the possibility that iron may promote the development of liver cancer, it is desirable to avoid iron overload in HCV-infected patients on dialysis, and iron therapy should be reserved for those patients who cannot correct anemia even if they receive the maximum dose of ESA.

Chapter 5. ESA hyporesponsiveness

1) Patients with ESA hyporesponsiveness are likely to have poor prognoses.

2) The factors underlying ESA hyporesponsiveness should be carefully examined in patients who show initial or subsequent hyporesponsiveness to ESA.

3) ESA hyporesponsiveness should be defined on the basis of the results of a prospective study examining the association between the prognosis and certain indices (for initial ESA responsiveness, the index is calculated from changes in hemoglobin levels (ΔHb), measured after a certain period from the administration of a certain amount of weight-based ESA dosing). However, such data are not currently available. Therefore, defining ESA hyporesponsiveness with numerical values is difficult.

4) Patients are possibly hyporesponsive to ESA if their Hb level does not increase or the target Hb level is not maintained with the regimen or dose approved under the health insurance system in Japan.

Rationale

(1) ESA hyporesponsiveness and prognosis

Recently, poor prognoses of patients with ESA hyporesponsiveness have emerged. Whether the clinical condition that causes ESA hyporesponsiveness is the contributing factor of poor prognoses or whether high doses of ESA administered to patients with ESA hyporesponsiveness to achieve a target Hb level adversely affect their prognoses has not been clarified. However, the appropriate diagnosis of patients with ESA hyporesponsiveness is expected to improve the background clinical conditions related to poor diagnosis and to improve their prognosis via an optimal ESA regimen.

In the secondary analysis of the TREAT study, in which the primary analysis aimed to examine the effect of high target Hb level with ESA treatment on cardiovascular events and mortality in 4038 predialysis CKD patients with type 2 diabetes, the relationship between initial ESA hyporesponsiveness and prognosis was examined. Patients were administered an initial dose of 0.75 μg/kg body weight of DA once every 2 weeks (i.e., at weeks 0 and 2). The changes in Hb levels after 4 weeks were categorized into quartiles. Patients with the lowest quartile, who had a <2% increase in Hb, had significantly higher rates of death and cardiovascular events compared to those with better responses during the observation period (median, 29.1 months) [169]. Furthermore, in the secondary analysis of the Normal Hematocrit Cardiac Trial, which included 1233 HD patients with a history of heart failure or ischemic heart disease, hyporesponsiveness to ESA was defined as the ratio of weekly Ht change per epoetin-α dose increase during weeks 1–3 after a dose escalation of epoetin-α in 321 out of 618 patients assigned to the normal Ht group. The results indicated that patients with the lowest quartile of the ratio showed negligible increases in Hb levels and had significantly higher mortality rates in 1 year than patients with the highest quartile [135]. In addition, the usefulness of the ESA resistance index (ERI) as a measure of ESA responsiveness during the maintenance phase of ESA treatment has also been reported. In a cohort study of 753 HD patients performed in Italy, patients were categorized into quartiles according to ERI [ESA dose/(body weight × Hb level)], and the results showed that the patients with the highest ERI had 1.6-fold and 1.4-fold higher all-cause mortality rates and fatal or nonfatal cardiovascular events, respectively, than patients in the other groups [170].

(2) Factors reducing ESA responsiveness

Although ESA responsiveness varies widely among CKD patients, approximately 10% of CKD patients show poor responsiveness to ESA [171]. This variation in response to ESA results from the fact that anemia in CKD patients is not always equal to renal anemia. The definition of renal anemia is anemia caused by an absolute or relative decrease in EPO production in the kidneys, and the main cause of this is CKD. Generally, the level of anemia in CKD patients also depends on deficiencies in iron and/or various vitamins, complications of CKD (e.g., gastrointestinal bleeding, malignant tumors, infections), secondary diseases of CKD (e.g., secondary hyperparathyroidism),

and factors associated with dialysis therapy (Table 6). Hematological disorders, such as MDS, should also be considered (especially in the elderly). These factors necessarily have a considerable effect on ESA responsiveness [15]. Therefore, factors that may attenuate ESA responsiveness should be excluded, as much as possible, before the start of ESA therapy for CKD patients. However, in daily clinical practice, it is difficult to completely exclude such factors. Therefore, when initial or subsequent ESA hyporesponsiveness is observed, the causes of hyporesponsiveness should be identified as soon as possible rather than increasing the ESA dose to increase the Hb level.

(3) Definition of ESA hyporesponsiveness

In principle, ESA hyporesponsiveness should be defined on the basis of the results of prospective studies examining the association between prognosis and certain indices (for initial ESA responsiveness, the index is calculated from ΔHb, measured after a certain period from the administration of a certain amount of weight-based ESA dosing). However, the definitions of ESA hyporesponsiveness in conventional guidelines were not based on the scientific evidence derived from studies examining prognosis in relation to ESA responsiveness.

For example, the EBPG guidelines for anemia (2004) defined ESA hyporesponsiveness as: "Hb level is not achieved to or is not maintained at target Hb level (11–12 g/dL) despite the use of 300 IU/kg per week (20,000 IU/week) of epoetin or 1.5 μg/kg per week (100 μg/week) of DA" [172]. The Kidney Disease Outcomes Quality Initiatives (KDOQI) guidelines (2006) defined it as: "Hb level of ≤11 g/dL despite the use of 500 IU/kg per week of epoetin" [173]. These values were not based on the evidence from studies evaluating the prognoses of patients in relation to ESA responsiveness. The 2008 JSDT Guidelines for Renal Anemia in Chronic Kidney Disease defined ESA hyporesponsiveness by incorporating the information in the package inserts of ESA: under the condition that there is no iron deficiency, (1) for HD patients, a failure to achieve anemia correction and the target Hb level despite the use of 3000 IU/dose of intravenous rHuEPO three times per week (9000 IU/week) or 60 μg/week of intravenous DA once per week; (2) for PD patients, a failure to achieve anemia correction and the target Hb level despite the use of 6000 IU/dose of subcutaneous rHuEPO once per week (6000 IU/week) or 60 μg/week of intravenous DA once per week; (3) for predialysis CKD patients, a failure to achieve anemia correction and the target Hb level despite the use of 6000 IU/dose of subcutaneous rHuEPO once per week (6000 IU/week) [15]. As in the EBPG and KDOQI guidelines, these values were not based on scientific evidence. The KDIGO guidelines published in 2012 defined ESA hyporesponsiveness as: "Hb level not improved even after the first month of ESA treatment on appropriate weight-based dosing" [32]. This is the first absolute definition of ESA hyporesponsiveness in association with the prognosis of patient, and was based on the results of a secondary analysis of the TREAT study.

The backgrounds of patients enrolled in the TREAT study and Normal Hematocrit Cardiac Trial were markedly different from those of CKD patients in Japan. Therefore, applying the results of the secondary analyses of these trials to renal anemia treatment for CKD patients in Japan is difficult. For example, patients enrolled in the TREAT study had a small amount of proteinuria (0.4 g/gCr) regardless of their serum Cr levels of approximately 1.8 mg/dL, and approximately 65% of them had CVD. Therefore, systemic atherosclerosis caused by diabetes might be advanced in these patients, which might have led to CKD. Similarly, the patients enrolled in the Normal Hematocrit Cardiac Trial had ischemic heart disease or heart failure, 66% of them had an arteriovenous graft for vascular access, and the Ht level remained at ~30% regardless of the administration of epoetin at ~160 IU/kg/week before a dose escalation of epoetin-α, indicating that

Table 6 Factors of erythropoiesis-stimulating agents hyporesponsiveness

Bleeding and blood loss	Gastrointestinal bleeding, menses, blood trapping in the dialyzer
Hematopoietic disorder	Infections (including blood access infection and peritoneal access infections), inflammation, autoimmune disease Aluminum poisoning, lead poisoning, severe hyperparathyroidism (osteitis fibrosa) Under dialysis Renin–angiotensin system (RAS) inhibitor Malignant tumor
Deficiency of elements required for erythropoiesis	Iron deficiency (copper deficiency, vitamin C deficiency), folic acid deficiency, vitamin B12 deficiency
Hematopoietic organ tumor and hematological disorder	Multiple myeloma, hemolysis, abnormal hemoglobin disease
Hypersplenism	
Anti-EPO antibody	
Other factors	Zinc deficiency, carnitine deficiency, vitamin E deficiency

Cited from [5], partially revised

the responsiveness to ESA in these patients was poor at baseline. From the aforementioned results of these secondary analyses, ESA hyporesponsiveness itself possibly indicates poor diagnosis; however, we cannot exclude the possibility that (1) the administration of high doses of ESA compared with those in Japan (TREAT, ~230 μg/month; Normal Hematocrit Cardiac Trial, ~450 IU/kg/week) and (2) maintaining a high target Hb level for patients with a specific background may affect the prognoses of patients.

The secondary analysis of the CHOIR study, in which the primary analysis aimed to compare the differences in prognosis (including the onset of CVD) in 1432 predialysis CKD patients, in which 35% of patients were complicated with CVD, classified patients into two groups: normal Hb level with ESA treatment (normalized Hb group) and conventional target Hb level (conventional Hb group). This report indicated that the incidence of cardiovascular events and the frequency of high-dose ESA use (epoetin-α, ≥20,000 IU/week) were low in patients who achieved the target Hb level at 4 and 9 months after the start of administration among the normalized Hb group; in contrast, these indices were high in the patients who did not achieve the target Hb level (Fig. 2) [45]. In addition, another secondary analysis using the database of the CHOIR study indicated that the administration of >10,095 IU/week of epoetin-α was related to cardiovascular events and death regardless of the Hb level achieved 4 months after the start of ESA administration, indicating that the ESA dose is the most important factor in predicting prognoses [174].

The results of a meta-analysis on the relationship between ESA dose and the prognoses of CKD patients revealed that an ESA dose (epoetin-α equivalent) of ≥10,000 IU/week in the first 3 months after the start of ESA administration is an independent predictor of all-cause mortality [incidence rate ratio (IRR), 1.42; 95% CI, 1.10–1.83]. The relationship between the ESA dose of the entire treatment period and prognosis was similar (IRR, 1.09; 95% CI, 1.02–1.18). The risk remained significant when the data were adjusted for the target Hb level [175]. According to the registry data of dialysis patients in Japan, the ESA dose is an independent predictor of 1-year all-cause and cardiovascular mortality. This tendency is more remarkable in patients with low Hb levels. In patients with Hb levels of <10 g/dL, an ESA dose (epoetin-α equivalent) of ≥6000 IU/week increased the all-cause mortality risk by 1.94-fold and the cardiovascular mortality risk by 2.02-fold [176]. From these reports, the ESA dose and prognoses of CKD patients are considered to be highly related. However, the backgrounds of patients enrolled in the CHOIR study were markedly different from those of CKD patients in Japan; thus, these results cannot be directly applied to the treatment of renal anemia in CKD patients in Japan. However, it is reasonable to reduce the ESA dose to as low as possible for patients complicated with atherosclerotic diseases, including diabetes, considering the balance with the target Hb level. Recently, conventional rHuEPO has been gradually replaced with long-acting ESAs (DA and CERA), and it is not reasonable to assume that the equivalent, determined by the conversion rate with respect to epoetin, has the same effect on erythropoiesis and other cells as epoetin.

As explained above, defining ESA hyporesponsiveness and high-dose ESA by numerical values is difficult at this time because of the differences in the backgrounds of CKD patients; the treatment of renal anemia (e.g., ESA dose) in Europe, the USA, and Japan; the absence of a uniform evaluation method of ESA responsiveness (e.g., ESA dose and evaluation period); and differences in the type of ESA used.

Chapter 6. Side effects and concomitant symptoms of ESAs

The treatment of renal anemia has been significantly improved with the emergence of ESAs. However, various

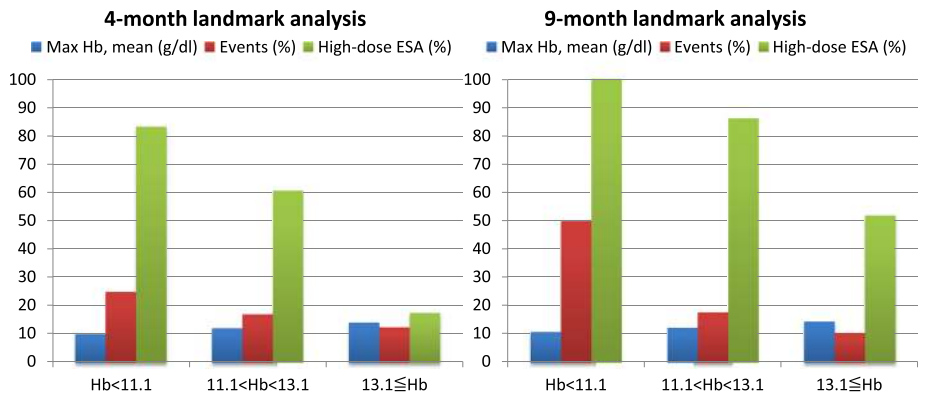

Fig. 2 Secondary analysis of the Correction of Hemoglobin and Outcomes in Renal Insufficiency trial: erythropoiesis-stimulating agent dose and prognosis. Status of the achievement of target hemoglobin (Hb) level, incidence of events, and erythropoiesis-stimulating agent (ESA) dose of the normalized Hb group 4 and 9 months after the start of ESA administration (cited from [9], partially revised)

side effects and concomitant symptoms have been reported. Table 7 shows a summary of the typical side effects of ESAs and ESA-induced concomitant symptoms. Among them, the major side effects and concomitant symptoms that are supported by substantial evidence in the literature are explained in this chapter. In the latter half of this chapter, typical CQs are raised and the rationale for these questions is explained.

Rationale

Hypertension

Hypertension is a concomitant symptom induced by ESAs. In Europe and the USA, the rates of hypertension and blood pressure elevation during rHuEPO therapy are 20–30%. In Japan, the clinical data on rHuEPO and the clinical outcomes obtained after commercialization of rHuEPO showed that the rates were ~3–7% [177]. On the basis of domestic clinical test data, the frequencies of hypertension and blood pressure elevation during DA therapy were determined to be 11.1 and 6.0% [178] and those during CERA therapy were 6.0 and 1.2%, respectively [179].

Blood pressure elevation caused by ESAs is related to the control of anemia. The results of a meta-analysis demonstrated that patients who were treated with high target Hb levels frequently have hypertension [32]. The mechanisms behind the improvement in anemia and the incidence of hypertension are as follows: (1) dilated peripheral vessels contract as a result of the improved condition of tissues in the hypoxic state associated with the improvement in anemia and (2) reduced or insufficient cardiac output with respect to the increased resistance of peripheral vessels due to improved blood viscosity. Other reported factors include (3) the re-setting between the changes in body fluid volume associated with the improvement in anemia and the resistance of peripheral vessels, (4) the involvement of vasopressors such as endothelin, and (5) enhanced responsiveness to vasopressors such as angiotensin II. It has also been reported that patients with a family history and past history of hypertension tend to have hypertension because of the presence of risk for the disease [180]. A relationship between the inherited factors for hypertension and the T allele of M235T angiotensinogen gene polymorphism has also been reported [181].

Hypertension caused by the use of ESAs is frequently observed, particularly at the start of ESA therapy. It is recommended that the rate of improvement in anemia should be gradual while paying attention to blood pressure elevation [182]. According to the guidelines in Europe and the USA, the Hb level should be increased by 1–2 g/dL per month to improve anemia. According to the drug package insert for ESAs available in Europe and the USA, the ESA dose should be decreased when the Hb level increases by more than 1 g/dL per 2 weeks. ESAs should also be carefully administered, particularly in patients with a history of hypertension, to prevent marked blood pressure elevation. For HD patients, dry weight should be controlled if the circulating blood volume increases (excess body fluid volume), and an appropriate antihypertensive agent should be administered while confirming its efficacy.

When rHuEPO was first commercialized, cases of patients with suspected hypertensive encephalopathy caused by rapid blood pressure elevation were reported. However, the blood pressure of such patients has been appropriately controlled recently, and the frequency of this condition is now low.

Thromboembolism

Thromboembolism is a potentially concerning complication during ESA therapy. According to reports from other countries on the risk of thromboembolism, the increase in Hb level leads to increased risk of vascular access occlusion,

Table 7 Side effects and concomitant symptoms of erythropoiesis-stimulating agents

Item	Factor
Side effects that are supported by substantial evidence in the literature	
1. Hypertension	• Blood pressure may increase because of direct or indirect effects of ESAs.
2. Thromboembolism	• The incidence of thromboembolism may increase in patients with CVD complication because of the excessive improvement in anemia (normalization of Hb level).
	• An increase in the incidence of thrombosis was reported in cancer patients treated with ESAs.
3. Pure red cell aplasia (PRCA)	• PRCA develops as a result of the appearance of anti-EPO antibodies.
Side effects that are considered to be caused by ESA administration in addition to those listed above	
1. Increases in extracorporeal circulating residual blood volume and the required dose of anticoagulant	• These may result from the increase in blood viscosity associated with the excessive improvement in anemia.
2. Onset and development of solid cancer	• The results of basic research showed the association of ESAs with the onset and development of cancer.

death, and nonfatal cardiac infarction. In addition, the administration of ESAs to patients with solid cancers may increase the incidence of thrombosis (refer to the rationale on CQ6 later in the guidelines).

The results of a large-scale observation study on the development of thromboembolism associated with ESA administration indicated that in 2116 Japanese dialysis patients, the risk of thromboembolism increased with the administration of rHuEPO [183]. In addition, cases in which the causal relationship between ESA therapy and the development of thromboembolism cannot be denied have been reported, although the number of such cases is small. Studies in other countries demonstrated that the risk of vascular access occlusion (particularly in synthetic grafts) increases [30] as the Hb level is normalized [30, 31, 184]. In dialysis patients complicated with ischemic heart disease, heart failure, or uncontrolled hypertension, the normalization of Hb level is reported to lead to an increase in the risk of death and nonfatal cardiac infarction [30, 31, 185].

A Japanese study on the development of thromboembolism with the administration of DA indicated no relationship between the increase in Hb level and increased risk of thromboembolism [26]. On the basis of this finding, there is no medical evidence that can be applied to general Japanese dialysis patients regarding the development of thromboembolism as a complication of ESA therapy.

In the CHOIR trial in predialysis CKD patients, the target Hb levels of two groups were set at 13.5 and 11.3 g/dL. The frequencies of composite endpoints, such as death and cardiac infarction, were more significantly increased in the patients whose target Hb level was 13.5 g/dL [43]. In the TREAT study, the frequency of stroke was significantly higher in patients with high Hb levels [36]. Many patients with a history of cerebrovascular disease or CVD were enrolled in these studies, and the background characteristics of the patients were different from those of Japanese patients [186]. Care should be taken not to cause excessive erythropoiesis when ESAs are administered to high-risk patients who have complications or a history of vascular disease.

PRCA

Cases of PRCA caused by anti-EPO antibodies (neutralizing antibodies) after ESA administration have been reported. Since 1998, cases of secondary PRCA associated with the generation of anti-EPO antibodies after the administration of EPREX® (epoetin-α, Johnson & Johnson Pharmaceutical Research & Development, LLC) have been reported, mainly in Europe [187]. The frequency of PRCA in patients administered rHuEPO worldwide is extremely low; however, the frequency of PRCA caused by subcutaneous administration of rHuEPO is 33-fold higher than that caused by intravenous rHuEPO [188]. Although the mechanism of the development of PRCA has not been clarified, inappropriate syringe formulation and the method of administration (subcutaneous administration) rather than the antigenicity of endogenous EPO may be associated with the increased frequencies of PRCA.

There are reports of PRCA caused by formulations other than EPREX®: 0.02–0.16 per 10,000 patients for subcutaneous administration and 0.02 per 10,000 patients for intravenous administration [189]. Patients with PRCA were reported following the administration of epoetin-α and epoetin-β, which are commercially available in Japan, although the number of such patients was extremely small [190–192]. Cases of PRCA caused by the administration of DA have been reported in other countries [193, 194]. In addition, an agent with similar activity to ESA was reported to induce sudden PRCA in Thailand [195]. Considering the results of the above reports, it is possible that adverse events may be caused by the production of antibodies to ESAs, which are newly developed in Japan, requiring close observation.

CQ5: Should an anticoagulant or an antiplatelet drug be used in combination with an ESA when ESA is administered for the treatment of renal anemia in CKD patients with a history of thrombosis?

Statement 5

1) There is no evidence that the combined use of an anticoagulant or an antiplatelet drug with an ESA decreases the risk of thromboembolism. (not graded)

2) Combined use of aspirin with an ESA possibly suppresses the formation of thrombi in patients with the target Hb level in the range of 10–11 g/dL. (not graded)

Rationale

The efficacy of anticoagulants or antiplatelet drugs is unclear because no clinical studies have been performed regarding their preventive effect on thromboembolism caused by ESAs (outcome) in patients with renal anemia and a history of thrombosis.

In a RCT study targeting non-CKD patients, epoetin (rHuEPO) was administered to patients with acute myocardial infarction to protect their heart function, although this was a small-scale RCT and conducted over a short follow-up period [196]. In this report, factors related to rHuEPO administration and thrombosis in patients also treated with an antiplatelet drug were examined. The results indicated that rHuEPO administration did not affect the activation of platelets and vascular endothelial cells associated with thrombosis in patients also treated with an antiplatelet agent. In addition, one report assessed the relationship between aspirin administration and the

arteriovenous fistula survival in 2815 HD patients enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS) study [197]. Although the methods of ESA administration in the study were not reported in detail, the Hb levels of patients using aspirin were controlled at 10.4 g/dL, which was slightly higher than that of the control group (Hb level, 9.9 g/dL). This study demonstrated that aspirin administration significantly improved arteriovenous fistula survival.

These reports provide evidence that the combined use of an anticoagulant or an antiplatelet drug with ESAs for patients with renal anemia and a history of thrombosis, cerebrovascular disease, or CVD may be somewhat effective for preventing thrombosis. However, persistent use of an anticoagulant or an antiplatelet drug induces the tendency for bleeding and the risk of complications, such as gastrointestinal bleeding. In patients with a high risk of thromboembolism caused by ESA administration, the first choice is to avoid excessive erythropoiesis to prevent thromboembolism. When the use of an anticoagulant or an antiplatelet drug is considered, the risk of a complication should be considered carefully before administration.

CQ6: Should an ESA be used for renal anemia in patients with cancer?

Statement 6

1) ESA therapy in patients with cancer complicated with anemia, particularly in patients undergoing chemotherapy, may increase the risk of thrombosis and death. (not graded)

2) ESA therapy for renal anemia in patients with cancer may possibly increase the risk of thrombosis and death. (not graded)

Rationale

Approximately 50% of patients with solid cancers develop anemia. There are various causes of anemia in these patients, such as malnutrition, bleeding, hemolysis, and the proliferation of tumor cells in the bone marrow. Such patients with anemia are currently treated with ESAs; however, the survival period of some patients is short and the efficacy of ESAs has not been clearly demonstrated.

In basic research, the EPO receptor is reported to be expressed in not only hematopoietic stem cells but also tumor cells [198, 199]. There is a concern that direct EPO stimulation via the EPO receptor or an indirect mechanism such as an increase in the amount of oxygen supplied to tumor cells is associated with the proliferation/invasion of tumor cells, tumor cell lifetime, and anti-apoptotic action, affecting the sensitivity of tumor cells to radiation therapy.

The results of a recent meta-analysis indicated that ESA administration to patients with cancer increases the risk of death and the frequency of thrombosis [185, 200]. On the basis of these reports, the Food and Drug Administration in the USA called attention to ESA use in patients with cancer. The American Society of Hematology and the American Society of Clinical Oncology revised the guidelines related to ESA therapy for patients with cancer based on the results of a meta-analysis and RCT reported between 2007 and 2009. This report specified that ESAs should not be used for treating anemia in cancer patients undergoing chemotherapy, except in patients with MDS, and that the increased risk of thrombosis demands closer observation [201].

A clinical test of the onset and development of cancer induced by an ESA (outcome) targeting CKD patients with cancer has not been published. Therefore, whether ESAs should be used for renal anemia in patients with cancer has not been clarified. However, the results of the TREAT study with respect to the treatment of renal anemia targeting CKD patients with type 2 diabetes who were randomly assigned to receive DA or a placebo indicated that the incidence of stroke in patients treated with an ESA and the cancer mortality rate in patients with a history of cancer increased [36]. In the study, cancer was listed in the exclusion criteria; however, patients with unconfirmed cancer were enrolled, and the number of patients who developed a new cancer because of ESA use was not clarified. Seliger et al. reported that ESA use was associated with an increased risk of stroke among CKD patients, particularly in those with cancer [202]. In this study, the mean Hb levels of patients with and without cancer were equal. However, higher doses of ESAs were administered to patients with cancer, suggesting that a high dose of ESAs is associated with the increased risk of stroke.

In Japan, the relationship between the duration of the use of epoetin (rHuEPO; duration of rHuEPO use <6 or ≥6 months) and the incidence of thrombosis and cancer in patients with CKD stages 4 and 5 was examined on the basis of the results of the TREAT study. The results indicated that there was no clear relationship between the two [203]. However, the study was cross-sectional and limited because the results of three groups (patients who received epoetin for <6 and ≥6 months and no epoetin) were compared. Therefore, the results of the study did not provide sufficient evidence of the safety and efficacy of ESA therapy for renal anemia in patients with cancer.

When ESAs are used for renal anemia in patients with cancer to limit the need for blood transfusion, ESA overdose should be avoided, and the improvement in anemia and the risk of developing complications such as thrombosis should also be carefully monitored.

Chapter 7. Red blood cell transfusion

CQ7: Is transfusion effective for the treatment of renal anemia?

Statement 7

1) As maintenance therapy for renal anemia with sufficient dialysis, appropriate ESAs, and iron therapy, we recommend minimal red blood cell (RBC) transfusion to improve general condition and symptoms related to anemia. (1B)

2) For patients with rapidly progressing anemia and those who plan to undergo an operation that could induce bleeding, we recommend minimal RBC transfusion. (1B).

3) For patients with symptoms of persistent anemia and ESA hyporesponsiveness, we suggest minimal RBC transfusion. (2C)

4) For patients who cannot receive sufficient doses of ESAs because of collateral side effects, we suggest minimal RBC transfusion. (2C)

5) For patients who are candidates for renal transplantation, we recommend avoiding, when possible, RBC transfusion to minimize the risk of enhanced antibody production (sensitization), which may cause rejection after transplantation. (1C)

Rationale

The symptoms of renal anemia in dialysis patients have markedly improved due to improvements in dialysis efficiency, reduced blood loss during dialysis, and the appropriate administration of ESAs and iron supplements. As a result, the frequency of RBC transfusion in patients with CKD has decreased [204–206]. However, RBC transfusion is still required in certain conditions and will still be necessary in the future. RBC transfusion is a palliative therapeutic modality, and not a definitive treatment. Careful prior evaluation to determine the possible improvement in clinical symptoms by transfusion should be carried out before RBC transfusion [207]. RBC transfusion should be performed only when the advantages are considered to exceed the disadvantages, and the blood volume for transfusion should be as low as possible [32].

(1)Indications for RBC transfusion

Indications for RBC transfusion are restricted to the following cases:

- Chronic anemia (including severe anemia), extreme ESA hyporesponsiveness, and difficulty in administering a sufficient dose of ESA because of collateral side effects.
- Acute anemia (including rapidly advancing anemia because of bleeding), hemolysis, or a surgical reason.

Generally, the symptoms of chronic anemia are not clear and depend on the presence of complications and daily and social activities of patients. Therefore, the timing of the treatment of anemia by RBC transfusion should be determined considering the target Hb level. The condition of each patient should be carefully observed, and the blood volume for transfusion should be as low as possible [21, 207–210]. Before RBC transfusion, written informed consent should be obtained by practitioners after explaining the necessity and risks of RBC transfusion to the patient in an easy-to-understand manner. Indications for RBC transfusion are summarized in Table 8.

(2)Cautions for RBC transfusion

RBC transfusion should be performed with caution to avoid performing ABO-incompatible blood transfusion, which may cause very serious symptoms, such as hemolytic anemia and blood coagulation abnormalities. In addition, various side effects associated with RBC transfusion should be carefully observed. Typical side effects include excessive body fluid volume (congestive heart failure), hyperkalemia, hemolytic adverse reactions, allergic reactions/anaphylaxis, transfusion-related acute lung injury, infection, iron overload, graft-versus-host disease, citrate intoxication associated with massive blood transfusion, and sensitization by major histocompatibility complex (MHC) antigen [207, 211–214].

The Japanese Red Cross Society supplies red blood cell concentrates that have been treated with leukocyte removal filters [214]. However, this treatment cannot completely eliminate the sensitization of MHC antigens that results from trace amounts of white blood cells remaining in the concentrates [211–213]. According to a report on the history of transfusion and the rate of positivity for human leukocyte antigen (HLA) antibodies, the levels of anti-HLA antibodies increase by approximately 4-fold after transfusion [215]. The decision to perform RBC transfusion in patients who are candidates for organ transplantation should be carefully considered. When surgery requiring RBC transfusion is planned, measures such as intraoperative autotransfusion may be required in addition to hematopoiesis by prior planned administration of ESAs and planned collection and storage of blood.

Table 8 Cases requiring red blood cell transfusion

Patients with severe anemia with signs/symptoms related to anemia
Patients with acute blood loss associated with unstable hemodynamics
Patients undergoing surgery with excessive blood loss
Patients with extreme ESA hyporesponsiveness
Patients who cannot receive a sufficient dose of ESA because of side effects

Chapter 8. Renal anemia in pediatric patients

1. Diagnosis and criteria of renal anemia in pediatric patients

1) Hb level should be used as a reference for the diagnosis of anemia in children. The following are the appropriate reference Hb levels for the diagnosis of anemia in the pediatric population according to age and gender.
Age (gender) Hb level
0.5–5 years <11.0 g/dL
5–12 years <11.5 g/dL
12–15 years <12.0 g/dL
>15 years/male <13.0 g/dL
Female <12.0 g/dL

2) Renal anemia is mainly caused by decreased EPO production associated with CKD. The diagnosis of renal anemia is made when CKD alone is the primary cause of anemia and there are no other diseases that can cause anemia.

Rationale

Anemia is a major complication of CKD in children and adults. The prevalence of anemia in children with CKD increases as the CKD stage advances. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) show that the prevalence of anemia in children with CKD stages 3, 4, and 5 was ≥73, ≥87, and ≥93%, respectively [216], indicating that renal anemia develops in the early stage of CKD.

The physiological Hb levels in the healthy population vary within a wide range depending on age, gender, and race. In children, whose body size changes greatly, an accurate evaluation of the reference Hb level for the diagnosis of anemia is required and is more important than that in adults. In the 2008 JSDT Guidelines for Renal Anemia in Chronic Kidney Disease (2008 JSDT guidelines) [15], we adopted the reference Hb level given in the National Health and Nutrition Examination Survey (NHANES) III for children aged ≥1 year old, and that given in Nathan and Orkin's textbook of pediatric hematology (6th edition) for children aged <2 years. In 2008, the World Health Organization (WHO) reported the reference Hb levels for adults and children [217], which were adopted in the KDIGO guidelines published in 2012. In the 2015 JSDT guidelines, we also adopted the reference Hb levels given by the WHO [217].

In Japan, no systematic large-scale epidemiological survey has been performed, such as the NHANES III study in the USA. However, the reference ranges of Hb levels in the Japanese population were determined by the latent reference value extraction method using 66,261 samples obtained from one facility, as shown in Table 9 [218]. In this table, the 2.5–97.5 percentiles are treated as the reference values. In the 2015 JSDT guidelines, we adopted these values as the Japanese reference values and presented them with the WHO reference values [217].

Renal anemia is mainly caused by decreased EPO production associated with CKD. In addition, various other factors, such as the suppression of erythropoiesis, the shortening of RBC lifespan, disorders of iron metabolism, blood loss through dialysis circuits, bleeding, and malnutrition, are expected to contribute to anemia. For details, refer to Chapter 1 ("Diagnosis of renal anemia") of these guidelines. Malnutrition in the pediatric period, during which children experience significant growth and development, is a serious problem. Vitamin B_{12}, folic acid, vitamin C, and carnitine greatly affect the formation of normal mature RBCs, and deficiencies of these nutrients cause anemia in addition to iron deficiency. Therefore, proper nutritional management, including the supplementation of these nutrients, is essential [219].

Finally, various blood diseases that may cause anemia should be considered in the differential diagnosis of renal anemia. For details, refer to Chapter 1 ("Diagnosis of renal anemia").

CQ8: Target Hb level to be maintained during therapy for renal anemia in pediatric patients and criteria for starting therapy

Statement 8

1) The target Hb level to be maintained during therapy for renal anemia in pediatric patients is 11 g/dL. The therapy should be started when the Hb levels are <11 g/dL in several test results. We suggest that the conditions of individual patients (e.g., attendance at preschool or primary school and learning and physical abilities) should be carefully considered before the start of the therapy. (2D)

Rationale

The 2008 JSDT guidelines state that ESA therapy should be started when the patient is diagnosed with anemia and Hb levels of <11 g/dL in several test results and recommend that the target Hb level to be maintained during ESA therapy is ≥11 g/dL [15].

To the best of our knowledge, there are no RCTs in which the efficacy of ESAs in children has been examined. Therefore, the target Hb levels for children receiving ESA therapy have to be determined based on data from clinical observational studies of children and adults.

According to reports on children, those with Hb levels of <11 g/dL have a greater risk of death, a higher probability of hospitalization within 1 year after the start of dialysis [220], a significantly higher probability of left ventricular hypertrophy [221], and lower QOL [222] than children with Hb levels of ≥11 g/dL. Moreover, analysis of the International Pediatric Peritoneal Dialysis Network (IPPN) data conducted in 2013 revealed that the survival rate of children with Hb levels of <11 g/dL was significantly lower than that of children with Hb levels of ≥11 g/dL [223]. Therefore, we consider that in the 2015 JSDT guidelines, the target Hb levels for children undergoing therapy for

Table 9 Reference hemoglobin levels in Japanese children according to age and gender

Hb level/boy	Lower limit	Median	Upper limit	Hb level/girl	Lower limit	Median	Upper limit
0~1M	8.7	11.5	13.5	0~1M	8.7	11.5	13.5
1~2M	9.0	11.3	13.5	1~2M	9.0	11.3	13.5
2~3M	9.3	11.3	13.6	2~3M	9.3	11.3	13.6
3~4M	9.5	11.5	13.7	3~4M	9.5	11.5	13.7
4~5M	9.7	11.6	13.9	4~5M	9.7	11.6	13.9
5~6M	9.8	11.8	14.1	5~6M	9.8	11.8	14.1
6~7M	10.0	11.9	14.2	6~7M	10.0	11.9	14.2
7~8M	10.1	12.1	14.2	7~8M	10.1	12.1	14.2
8~9M	10.2	12.1	14.3	8~9M	10.2	12.1	14.3
9~10M	10.3	12.2	14.3	9~10M	10.3	12.2	14.3
10~11M	10.4	12.3	14.3	10~11M	10.4	12.3	14.3
11~12M	10.4	12.3	14.3	11~12M	10.4	12.3	14.3
1Y	10.5	12.4	14.1	1Y	10.7	12.4	14.1
2Y	10.7	12.6	14.2	2Y	10.9	12.7	14.2
3Y	11.0	12.7	14.2	3Y	11.1	12.8	14.2
4Y	11.2	12.9	14.2	4Y	11.2	12.9	14.2
5Y	11.4	13.0	14.3	5Y	11.3	13.0	14.3
6Y	11.5	13.0	14.4	6Y	11.5	13.0	14.4
7Y	11.7	13.1	14.5	7Y	11.6	13.1	14.5
8Y	11.8	13.2	14.6	8Y	11.7	13.2	14.6
9Y	11.9	13.3	14.8	9Y	11.8	13.2	14.7
10Y	12.0	13.4	15.0	10Y	11.8	13.3	14.8
11Y	12.1	13.6	15.4	11Y	11.9	13.4	14.9
12Y	12.2	13.9	15.7	12Y	11.9	13.4	14.9
13Y	12.3	14.1	16.0	13Y	11.9	13.4	14.9
14Y	12.5	14.3	16.2	14Y	11.9	13.4	14.9
15Y	12.6	14.6	16.5	15Y	11.8	13.4	14.9
16Y	12.8	14.8	16.7	16Y	11.8	13.4	14.8
17Y	13.0	15.0	16.8	17Y	11.7	13.3	14.7
18Y	13.2	15.2	17.0	18Y	11.6	13.3	14.6
19Y	13.4	15.3	17.1	19Y	11.6	13.2	14.6
20Y	13.7	15.4	17.2	20Y 1	11.5	13.2	14.6
		Number of samples, 10,127				Number of samples, 8409	

M monthes old, *Y* years old

renal anemia should be ≥11 g/dL, as in the 2008 JSDT guidelines.

In the KDIGO guidelines published in 2012, the upper limit of the target Hb level was set at 12 g/dL [87]. It has been reported that the risks of death and severe cardiovascular events increase in adult patients with Hb levels of ≥12 g/dL. However, applying this value to children, who are less likely to have arteriosclerosis or cardiovascular complications as basic diseases, may be problematic. The target Hb levels for children in the development period should be set considering indices such as growth, mental and physical development, attendance at preschool or primary school, and learning and physical abilities, which are different from the indices for adults [219, 224, 225]. In clinical practice, a comparison among three patient groups (Hb levels of <11, ≥11 and <12, and ≥12 g/dL) showed that QOL, including health state and physical functions, was a better index for patients with Hb levels of ≥12 g/dL [222]. Currently, data (efficacy and risk) related to the determination of the upper limit of target Hb levels are still scarce. In the 2015 JSDT guidelines, we consider that the target Hb level should be determined for individual

children considering their background by setting the lower limit at 11 g/dL, as in the 2008 JSDT guidelines.

The criterion for starting therapy for renal anemia is a Hb level of <11 g/dL for all patients in the 2008 JSDT guidelines [15]. The 2015 JSDT guidelines, however, suggest that therapy should be started according to not only the Hb level but also the conditions of individual patients (e.g., attendance at preschool or primary school and learning and physical abilities), as in the 2012 KDIGO guidelines [87].

2. Iron therapy for pediatric patients

1) For pediatric patients who are not receiving ESA or iron and cannot maintain the target Hb level, iron therapy should be considered prior to ESA therapy when the serum ferritin level is <50 ng/mL.

2) For pediatric patients who are receiving ESA and cannot maintain the target Hb level, iron therapy should be considered when the serum ferritin level is <100 ng/mL and TSAT is <20%.

3) For pediatric patients who are receiving ESA and cannot maintain the target Hb level, iron therapy should be considered when both of the following conditions are satisfied:
- Absence of diseases that decrease iron utilization rate.
- Serum ferritin level <100 ng/mL or TSAT <20%.

4) Attention and careful monitoring are needed to avoid iron overload when administering iron therapy.

Rationale

Pediatric patients with CKD tend to have iron deficiency in the early stages of CKD [226], and evaluation of the iron status and appropriate iron therapy are essential for the treatment of renal anemia in children. According to the 2008 JSDT guidelines [15], the 2012 KDIGO guidelines [227], and the comments on the 2012 KDIGO guidelines from the KDOQI [228], the criteria for starting iron therapy in pediatric patients with renal anemia are a TSAT of ≤20% and a serum ferritin level of ≤100 ng/mL. However, analysis of data from the Registry of the European Society for Paediatric Nephrology and the European Renal Association-European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry suggests that the optimal serum ferritin level in pediatric dialysis patients is in the range of 25–50 ng/mL [229]. In addition, a report on the IPPN Registry data showed that pediatric PD patients with serum ferritin levels of 10–25 ng/mL had the highest Hb levels [223]. In the 2015 JSDT guidelines, we set the following guidelines on the basis of the findings for adults: "For patients who are not treated with ESA or iron and cannot maintain target Hb levels, we suggest iron therapy prior to ESA therapy if the serum ferritin level is <50 ng/mL." "For patients who are treated with ESA and cannot maintain the target Hb level, we recommend iron therapy if the serum ferritin level is <100 ng/mL and TSAT is <20%." "For patients who are treated with ESA and cannot maintain target Hb levels, we suggest iron therapy if both the following conditions are satisfied: Absence of disease that decreases iron utilization rate, Serum ferritin level <100 ng/mL or TSAT <20%." These suggestions indicate that the disease in patients with a TSAT of <20% and a serum ferritin level of ≥100 ng/mL should be evaluated before the start of iron therapy to carefully determine the applicability of iron supplementation because such patients may have chronic inflammation or other causes of anemia that require attention. For details, refer to Chapter 4 ("Evaluation of iron status and iron therapy"). However, the findings in that chapter should be further examined for children in the future.

Very few studies have assessed the optimal serum ferritin levels for children during therapy for renal anemia. No findings have established the upper limit of serum ferritin level. Generally, however, the upper limit of serum ferritin level is considered to be 500 ng/mL [230]. Moreover, analyses of the ESPN/ERA-EDTA Registry data [229] and IPPN Registry data [223] have demonstrated that increasing the serum ferritin level to ≥200 ng/mL does not satisfactorily correct anemia. One study showed that the risk of infectious diseases increased when iron was supplemented in patients with sufficient iron stores [231]. Therefore, the necessity of iron supplementation should be carefully examined before the initiation of iron therapy.

As shown in the 2008 JSDT guidelines [15], iron supplements should, as a rule, be administered orally. However, iron should be administered intravenously if patients have difficulty in taking supplements orally, have malabsorption, or have not achieved the target TSAT or serum ferritin levels. The necessity and effectiveness of intravenous iron administration in HD patients have been studied. Iron supplementation at a dose of 2–3 mg/kg per day (maximum 6 mg/kg per day) should be administered in two to three divided doses. Gradual iron administration is necessary to prevent shock symptoms that may develop immediately after intravenous administration.

3. Method of ESA administration in pediatric patients (administration route and dose)

1) As a rule, rHuEPO should be administered subcutaneously as an initial single dose of 50–100 U/kg body weight per week. When anemia has been corrected, rHuEPO should be subcutaneously administered as a single dose of 100–200 U/kg once every 2 weeks as for maintenance.

2) DA should be administered intravenously to pediatric HD patients and subcutaneously or intravenously administered to pediatric PD and predialysis CKD patients. Initially, a single dose of 0.33 μg/kg (maximum 20 μg) is administered once per week to HD patients and 0.5 μg/kg (maximum 30 μg) once every 2 weeks to PD and predialysis CKD patients. When anemia has been corrected, a single dose of 5–60 μg is administered once per week to HD patients as maintenance therapy and 5–120 μg once every 2 weeks to PD and predialysis CKD patients. When the corrected condition is maintained, the interval between administrations can be extended to once every 2 weeks for HD patients and once every 4 weeks for PD and predialysis CKD patients. The starting dose should be 2-fold the maintenance dose, and the maximum single dose is 180 μg.

Rationale

The dose of rHuEPO required to achieve and maintain the target Hb level differs between adults and children. The NAPRTCS data show that a higher dose of rHuEPO is required for younger children [232]. This is thought to be because infants and children have a higher rHuEPO clearance rate [225]. Moreover, the required dose of rHuEPO depends on the dialysis method used; the required dose for pediatric PD patients is lower than that for pediatric HD patients [225]. A problem associated with rHuEPO therapy is the need for frequent subcutaneous or intravenous administration because of the agent's short half-life. In practice, the NAPRTCS report showed that 55% of pediatric PD patients and 85% of pediatric HD patients received rHuEPO at least twice per week [233]. The current guidelines for the dose of rHuEPO and dosing frequency should be further examined for pediatric patients to achieve and maintain their target Hb levels.

In Europe and the USA, the outcomes (e.g., dose, frequency, side effects) of DA therapy in children have been discussed, and its efficacy and safety have been reported [234, 235]. In particular, reports demonstrate that the dosing frequency of DA could be decreased because the half-life of DA is 3- or 4-fold longer than that of rHuEPO [234, 235]. For children, in whom physicians should consider pain reduction, medication compliance, and reduction in the burden on family members, the expanded application of DA therapy is predicted to occur in Japan [15]. Recently, in Japan, the efficacy and safety of DA have been examined in a study of pediatric PD patients [236] and a study of pediatric predialysis CKD, PD, and HD patients [237]. The former study showed that 88% of PD patients achieved their target Hb levels and 60% had their dosing frequency lowered to once every 4 weeks [221]. The latter study showed that all predialysis CKD, PD, and HD patients achieved their target Hb levels, with 64.5% of them maintaining the target Hb levels until the end of the observation period and 37.9% having their dosing frequency lowered to once every 4 weeks [237]. On the basis of these results, the administration of DA to children was started in Japan in September 2013. The NAPRTCS data show that the percentages of PD and HD patients who received DA increased by 21 and 19% from 2004 [233].

An increasing number of studies have examined the outcomes (e.g., dose, frequency, side effects) of CERA therapy in children, which was developed as a long-acting ESA [238, 239]. The decrease in dosing frequency in children may be beneficial not only for reducing the burden on medical workers and increasing safety, as in adults, but also for improving medication compliance and reducing the burden on family members. In Japan, the results of a phase III trial were reported in 2011 [240], and the use of CERA in dialysis adult patients with renal anemia was approved in July 2011. However, the use of CERA in children has not yet been discussed. Some approaches to expanding the use of CERA in children are needed.

4. ESA hyporesponsiveness in pediatric patients

1) ESA hyporesponsiveness is mostly caused by absolute or functional iron deficiency. When iron deficiency is not detected, physicians should search for the reasons and suspect chronic inflammation, malnutrition, inappropriate dialysis, hyperparathyroidism, and medication nonadherence.

Rationale

ESA hyporesponsiveness is observed in pediatric patients. According to the NAPRTCS data, at least 20% of pediatric patients with stage 4 CKD who are on ESA therapy have chronic anemia [216]. One report showed that ESA hyporesponsiveness in children is associated with chronic inflammation, malnutrition, and inappropriate dialysis [241]. In addition, analysis of the IPPN Registry data showed that the risk factors for not achieving or maintaining the target Hb level were high serum ferritin level, chronic inflammation, high parathyroid hormone level, hypoalbuminemia, use of PD solution with low biocompatibility, overhydration, deterioration of residual renal function, and low PD fluid turnover [223]. Thus, providing appropriate dialysis is essential for children to maintain ESA responsiveness. Attention should also be paid to medication nonadherence in children [219]. For details on ESA hyporesponsiveness, refer to Chapter 5 ("ESA hyporesponsiveness").

5. RBC transfusion in pediatric patients

1) The RBC transfusion protocol for children should be the same as that for adults.

6. Side effects and concomitant symptoms of ESAs in pediatric patients

1) The side effects of ESAs include hypertension, thromboembolism, and PRCA. Attention should be paid to these side effects in children.

Rationale

It has been shown by one report that the incidence of ESA-induced hypertension in pediatric dialysis patients was as high as ~30% and that it tended to be higher in patients who received high doses of ESA [242]. In particular, a rapid increase in Hb level has been reported to cause hypertension in children [242]. Therefore, anemia in children should be gradually corrected at a moderate rate, while paying close attention to any elevation in blood pressure. Careful ESA administration and observation are required for patients with hypertension.

One report showed that a small number of pediatric patients developed PRCA due to anti-EPO antibodies [243]. Other reports have demonstrated that PRCA is improved by stopping ESA therapy and administering immunosuppressive agents such as steroids [244, 245]. Physicians are required to fully explain to patients and their family members that ESA therapy is associated with such side effects but that they are rare and the risks are outweighed by the benefits of therapy.

According to a recent analysis of the IPPN Registry data [223], the risk of death was significantly higher in pediatric patients who received high doses of ESA (≥6000 U/m^2 per week) regardless of Hb level. When ESA responsiveness decreases and the dose of ESA is repeatedly increased, the patient's condition should be carefully observed.

For details of the side effects of ESA and ESA-induced collateral symptoms, refer to Chapter 6 ("Side effects and concomitant symptoms of ESAs").

Chapter 9. Post-transplant anemia in renal transplant recipients

1. Diagnosis and criteria for post-transplant anemia (PTA)

1) Hb level is used as a diagnostic index for PTA. PTA in adults is defined as Hb levels <13 g/dL in males and <12 g/dL in females.

2) There are various causes of PTA, such as allograft dysfunction, rejection episodes, infections, iron deficiency, and bone marrow suppression by immunosuppressive agents. Physicians should carefully identify the causes and prescribe appropriate treatment before starting anemia treatment.

3) The late phase of PTA (≥6 months after transplantation) is the main target of therapy for PTA.

Rationale

The annual number of renal transplant recipients has increased to ≥1600, exceeding the total number of PD patients [246]. Renal transplantation has been established as a renal replacement therapy in Japan and was added to the 2015 JSDT guidelines, which are currently being revised. To determine the target Hb level in renal transplant recipients for the first time, we epidemiologically investigated when to diagnose PTA and attempted to define the Hb level in PTA considering the specialty of renal transplantation that surgically removes the natural history of CKD.

In many papers, PTA in adults is defined as Hb levels <13 g/dL in males and <12 g/dL in females, similar to anemia defined by the WHO [247–254]. This definition is also adopted in the American Society of Transplantation guidelines [255]. Since renal transplant recipients have anemic conditions different from renal anemia because of their immunosuppressive state in addition to CKD, the definition of PTA in the references are adopted in the 2015 JSDT guidelines.

The early phase of PTA (<6 months after transplantation) is caused by complications such as renal anemia in the dialysis phase as a basic symptom, perioperative bleeding, and post-transplantation symptoms such as bone marrow suppression due to immunosuppressive agents used at relatively high doses, delayed graft function, frequent blood collection, and iron deficiency. The late phase of PTA (≥6 months after transplantation) is caused by infections, inflammation, and allograft dysfunction. Immunosuppressive agents, antihypertensive agents (angiotensin-converting enzyme inhibitors, e.g., angiotensin-converting enzyme; angiotensin-receptor blockers, e.g., ARB), iron deficiency, hemolysis, and malignant tumors also result in anemia. Among infections, parvovirus B19 causes post-transplantation pure red cell aplasia [256]. Among immunosuppressive agents, inhibitors of nucleic acid synthesis (e.g., mycophenolate mofetil, azathioprine, mizoribine) are particular causes of bone marrow suppression throughout the post-transplant course [247]. Physicians should first identify the causes of anemia from the various possibilities, such as those mentioned above, and prescribe treatment for any reversible factor before starting ESA therapy. In these guidelines, we use the term "post-transplantation anemia" (PTA) in renal transplant recipients instead of post-transplantation renal anemia because PTA is so unique that it should be treated differently from renal anemia, which is mainly caused by decreased production of EPO. Some reports have shown that there was no correlation between endogenous EPO level and PTA [247, 250].

The early phase of PTA is a risk factor for cardiovascular events and death and correlates with the loss of graft function [251, 257]. However, descriptions of discontinuity, continuity, and restarting of ESA therapy prescribed before transplantation are not given in the KDIGO [258] or European guidelines (Expert Group on Renal Transplantation, EBPG guidelines 2002) [259]. Both an observational study [260] and RCT study [261] demonstrated that ESA therapy for early PTA does not affect the prognoses of renal transplant recipients and that anemia in most recipients was resolved 8–12 weeks after transplantation. For patients with early PTA, maintaining appropriate immunosuppression to prevent rejection episodes is more important than prescribing anemia treatment.

In contrast, late PTA is detected at high rates of 30–40% in renal transplant recipients [262], and it continues during the post-transplant course. The prevalence of PTA shows no significant difference between deceased- and living-donor renal transplantations [250, 252] and negligible difference between genders. The prevalence of

PTA is 10 times higher than that in CKD stage-matched predialysis patients [262]. As renal function deteriorates, the prevalence of anemia in renal transplant recipients increases compared with that in non-transplant patients. Various clinical epidemiological studies on PTA have focused on late PTA [247, 250, 252, 262, 263]. Therefore, these guidelines basically provide target Hb levels for late PTA.

CQ9. What are the target Hb levels to be maintained in PTA patients?

Statement 9

1) For renal transplant recipients with late PTA who will start ESA therapy, we suggest that the target Hb level to be maintained by ESA therapy should be <13 g/dL. (2D)

2) For renal transplant recipients with late PTA who will start ESA therapy, we suggest that the target Hb level be set by referring to the above value and considering the conditions of individual patients in clinical practice. (2C)

Rationale

There are two representative clinical studies on ESA therapy for late PTA: a retrospective observational study conducted in 2009 and a RCT conducted in 2012. In the retrospective observational study [253], 1794 renal transplant recipients were divided into the ESA and non-ESA groups using the date of transplantation as a reference. They were followed up for 5.5 years on average. The results showed that the increase in Hb level to ≥14 g/dL significantly increased the risk of death in the ESA group when the Hb level of 12.5 g/dL was set as the reference level for low risk, while this tendency was not observed in the non-ESA group. Therefore, the increased risk was attributed to the side effects of ESAs, in concordance with the results of conventional large-scale studies. In this analysis, the risk of death in the ESA group was compared with that in the non-ESA group (as the control). The results showed that the risk of death reached ≥1 when the Hb level exceeded 13 g/dL. Therefore, the target Hb level during ESA therapy for PTA was considered to be <13 g/dL. It should be noted that in this previous observational study, non-ESA patients who needed to start ESA therapy after transplantation (284 of 989 patients) were counted as ESA patients, and neither the total ESA dose nor graft function of the two groups was described. This study involved spline curve analysis and was limited in the ways outlined above. Therefore, we could not accurately determine that the appropriate target Hb level is 13 g/dL.

The Correction of Anemia and Progression of Renal Insufficiency in Transplant patients (CAPRIT) study [264] was a French prospective multicenter interventional RCT on ESA therapy for late PTA. The subjects consisted of 125 patients with PTA without iron deficiency. They were divided into two groups on the basis of the target Hb level: the high Hb level group (13–15 g/dL; mean achieved Hb level, 13 g/dL) and the low Hb level group (10.5–11.5 g/dL; mean achieved Hb level, 11 g/dL). A 2-year follow-up assessment revealed that the GFR remained significantly higher in the high Hb level group. Because the achieved Hb level in the high Hb level group was 13 g/dL, this value was considered to be the appropriate upper limit of the target Hb level in ESA therapy. The CAPRIT study was a prospective RCT study but involved only a short-term (2-year) follow-up with GFR maintenance as the endpoint; the evidence level for the target Hb level in PTA is therefore still low.

The above retrospective and prospective studies targeted relatively young, active renal transplant recipients. In Japan, renal transplantation is performed for patients with a long dialysis vintage, unlike in Europe and the USA, and the mean waiting period is 15.4 years for deceased-donor renal transplantation (The Japan Society for Transplantation Factbook) [246]. A higher Hb level may be required to improve the QOL of renal transplant recipients with a dialysis vintage ≤10 years, including those who received preemptive renal transplantation, which is considered to be a low-risk remedy in Japan [265]. We attempted to stratify anemia treatment on the basis of individual risks, such as the risk of death after renal transplantation in patients with different dialysis vintages [227, 265, 266] and those with/without diabetes [267]. However, no strong evidence for this stratification is available to date, and only the target Hb level of <13 g/dL is provided in the guidelines. Moreover, transplant recipients experience chronic inflammation as a rejection episode, and for many of them, it is difficult to achieve the upper limit of the target Hb level in the presence of immunosuppressive agents in clinical practice. Therefore, we suggest that in clinical practice, the target Hb level should be set for individual patients who start ESA therapy in accordance with their conditions, such as dialysis vintage, the primary disease underlying end-stage renal failure, subjective symptoms, cardiovascular complications, allograft dysfunction, and the doses of the immunosuppressive agents being used.

CQ10. What are the criteria for starting PTA treatment?

Statement 10

1) For patients with late PTA, we suggest that anemia treatment should be started when the Hb level is <11 g/dL in multiple tests. (2D)

2) We recommend that RBC transfusion be avoided except for clinically inevitable cases to prevent unnecessary antibody production, which causes rejection episodes due to allosensitization. (1C)

Rationale

Setting the lower limit of Hb level in transplant recipients is related to the decision to perform transfusion.

Many transplant recipients who are started on dialysis again have severe PTA. As a result of inevitable transfusion, unnecessary antibody production (sensitization) causing rejection episodes can be induced, which markedly worsens the secondary outcomes of transplantation. For CKD predialysis and dialysis patients who are scheduled to receive transplantation, transfusion should be avoided for as long as possible. In particular, the risk of HLA sensitization after RBC transfusion is high in multipara and renal transplant recipients [213]. Therefore, setting the lower limit of Hb level to a higher value should be considered; however, there is no consensus on the Hb level at which transfusion is considered unnecessary in clinical practice. The TREAT study, a large-scale study of CKD predialysis patients, showed that the transfusion rate increased in the placebo group with a mean Hb level of 10.6 g/dL [36]. Moreover, the transfusion frequency decreased by 10% in the ESA group with a mean Hb level of 12.5 g/dL. The patients in this placebo group with Hb levels <9 g/dL were started on rescue therapy using ESAs. To avoid transfusion, however, it is not practical to start anemia treatment after the Hb level reaches the lower limit (<9 g/dL).

In the abovementioned CAPRIT study [264], five patients required transfusion in the low Hb group ($n = 59$) and one in the high Hb group ($n = 61$). In that study, the achieved Hb levels were 13 and 11 g/dL in the high and low Hb groups, respectively. Hence, the lower limit of the target Hb level should be set to ≥11 g/dL to avoid transfusion. Other observational studies have also shown that Hb levels <11 g/dL indicate the risk of loss of graft function and death [251, 257, 268, 269]. Therefore, a Hb level of <11 g/dL was set as the criterion for starting anemia treatment in these guidelines to avoid transfusion and to reduce the risks of loss of graft function and death.

Note that transfusion therapy is performed independently of any value of Hb level and should be appropriately administered in accordance with the clinical anemic conditions of individual patients during the course of various post-transplant complications (e.g., gastrointestinal bleeding and malignant tumors).

2. Iron therapy for PTA patients

1) The evaluation of iron status and iron therapy described in Chapter 4 should be adhered to.

Rationale

The most common type of early PTA is iron deficiency anemia [270]. Immediately after transplantation, it develops due to bleeding caused by surgery. It also develops because iron supplementation is frequently discontinued before transplantation and can be caused by blood collection during hospitalization. For female patients, menstruation restarts due to the changes in the endocrine environment after transplantation, resulting in iron deficiency anemia. Iron metabolism should be regularly evaluated.

Everolimus, a mammalian target of rapamycin inhibitor (mTORi), was developed as an alternative to calcineurin inhibitors (CNIs). A meta-analysis showed that another mTORi (sirolimus) is more likely to cause anemia than CNIs [271]. Sirolimus causes microcytic anemia via iron deficiency (by suppressing iron absorption in cooperation with hepcidin) [272]. Everolimus, which is available on the market in Japan, has also been reported to cause microcytic anemia [273].

The evaluation of iron status is important for PTA patients. TSAT and serum ferritin level are used as iron metabolism markers for grafts as in CKD patients, although their effectiveness in an inflammatory environment due to infections and rejection episodes is questioned [274, 275]. One report showed that there was no significant difference between the efficacy of oral and intravenous iron supplementation for PTA patients [276]. For details about administration methods, readers should refer to Chapter 4 ("Evaluation of iron status and iron therapy") of these guidelines. Further studies are required to clarify whether CKD and CKD transplantation can be treated the same with respect to the relationship between iron supplementation and infections.

3. ESA therapy for PTA patients

1) Subcutaneous administration of ESAs is mainly chosen.

2) The ESA administration route and dose described in Chapter 3 should be followed.

Rationale

Currently, only 10–20% of renal transplant recipients with severe late PTA (Hb levels ≤11 g/dL in males and ≤10 g/dL in females) receive ESA therapy [247, 252, 253]. The European and American guidelines on renal transplantation provide limited descriptions of the use of ESAs [255, 258, 259]. However, ESA therapy should be started for patients requiring anemia treatment after confirming that they have neither reversible factors nor absolute iron deficiency. Transplantation is performed with the assumption that the patients return to society and require subcutaneous administration of ESAs on an outpatient basis. Hence, the subcutaneous administration of long-acting ESAs, such as DA [277] and CERA [278], is frequently adopted. For details of ESA administration, readers should refer to Chapter 3 ("Administration method for ESAs—administration route and dose") of these guidelines.

4. ESA hyporesponsiveness in PTA patients

1) For patients with multifactorial PTA, physicians should search for the causes and prescribe appropriate treatment before starting anemia treatment if ESA hyporesponsiveness is detected.

Rationale

A report on the efficacy of DA in the treatment of PTA showed that 68% of patients who had received DA at a standard dose (0.75 μg/kg, once every 2 weeks) for 3 months had mild EPO-hyporesponsive anemia [277]. It was pointed out that the patients with ESA hyporesponsiveness showed deterioration of graft function and newly induced iron deficiency. Patients who received the optimal dose of an ESA but showed no increase in Hb level over baseline in the initial stage of ESA therapy may be hyporesponsive to ESA. ESA hyporesponsiveness is a strong predictor of the risks of CVD and death in transplant recipients [279]. For patients with multifactorial PTA, physicians should search for the causes and prescribe appropriate treatment before starting anemia treatment if ESA hyporesponsiveness is detected.

Abbreviations

ARB: Angiotensin II receptor blocker; BUN: Blood urea nitrogen; CARI: Caring for Australasians with Renal Impairment; CERA: Continuous erythropoietin receptor activator; CI: Confidence interval; CKD: Chronic kidney disease; CNI: Calcineurin inhibitor; Cr: Creatinine; CRP: C-reactive protein; CVD: Cardiovascular disease; DA: Darbepoetin alfa; DOPPS: Dialysis Outcomes and Practice Patterns Study; EBPG: European Best Practice Guidelines; EDTA: European Dialysis Transplantation Association; EPO: Erythropoietin; ESA: Erythropoiesis-stimulating agent; GFR: Glomerular filtration rate; Hb: Hemoglobin; HD: Hemodialysis; Ht: Hematocrit; IPPN: International Pediatric Peritoneal Dialysis Network; IRR: Incidence rate ratio; J-DOPPS: Japan Dialysis Outcomes and Practice Patterns Study; KDIGO: Kidney Disease: Improving Global Outcomes; KDOQI: Kidney Disease Outcomes Quality Initiatives; MCV: Mean corpuscular volume; MDS: Myelodysplastic syndromes; MHC: Major histocompatibility complex; MRI: Magnetic resonance imaging; mTORi: Mammalian target of rapamycin inhibitor; NAPRTCS: North American Pediatric Renal Transplant Cooperative studies; NHANES: National Health and Nutrition Examination Survey; PD: Peritoneal dialysis; PRCA: Pure red cell aplasia; PTA: Post-transplant anemia; QOL: Quality of life; RBC: Red blood cell; RCT: Randomized controlled trial; rHuEPO: Recombinant human erythropoietin; SD: Standard deviation; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey; SQUID: Superconducting quantum interference device; TIBC: Total iron binding capacity; TNF-α: Tumor necrosis factor-α; TSAT: Transferrin saturation; UIBC: Unsaturated iron binding capacity; WBC: White blood cell

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Authors' contributions

HY was in charge of Chapter 7 and generalized the manuscript as chairman of this guideline preparation committee. SN generalized the manuscript as vice chairman of the guideline preparation committee. TT contributed as chairman of the academic committee in the Japanese Society for Dialysis Therapy. IM contributed as chairman of the guideline preparation subcommittee in the Japanese Society for Dialysis Therapy. KS was in charge of Chapter 9. MN was in charge of Chapter 2 and Chapter 3. MH was in charge of Chapter 8. TS was in charge of Chapter 1. SM advised on the interpretation of medical statistics and bioinformatics. AA was in charge of Chapter 8. YI was in charge of Chapter 2 and Chapter 3. TK was in charge of Chapter 4. YK was in charge of Chapter 4. KS was in charge of Chapter 9. YT participated in coordination and helped to draft the manuscript. KT was in charge of Chapter 2 and Chapter 3. TH was in charge of Chapter 5. HHi participated in coordination and helped to draft the manuscript. HHo was in charge of Chapter 6. All authors read and approved the final manuscript.

Competing interests

The authors declare the following conflicts of interest:

Yasuhiko Ito: Received an honorarium for giving a lecture from, and belongs to a project endowed by, Baxter (a company that imports, produces, and sells dialysis products, plasma protein products, and drug administration systems).

Takahiro Kuragano: Received an honorarium for giving a lecture from Chugai Pharmaceutical Co., Ltd. (a company that produces, sells, and imports/exports prescription drugs).

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Consent for publication
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