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Clinical practice guidelines for anemia in chronic kidney disease: problems and solutions. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO)

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The development of clinical practice guidelines for the treatment of anemia in chronic kidney disease has been instrumental in identifying and reducing variations in the use of erythropoiesis-stimulating agents and iron replacement. Challenges to the effectiveness and safety of recommendations made in these guidelines were magnified when recent clinical trials showed no benefit or harm with respect to cardiovascular outcomes in subjects randomized to higher target hemoglobin levels. To address these concerns, Kidney Disease: Improving Global Outcomes (KDIGO) convened an international conference to examine the problems and shortcomings of existing anemia guidelines, which are a prime example of duplication of efforts to derive recommendations from a limited evidence base. The meeting was attended by representatives of the major guideline developing organizations, who agreed to avoid future duplicative efforts and to save resources in generating a common evidence report, whose recommendations could then be prioritized and implemented locally. This is a report to the international nephrology community of the recommendations for and timeline of the next anemia guidelines. It has been reviewed by the conference participants and approved as a position statement by the KDIGO Board of Directors.

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The introduction of erythropoietin into clinical practice in 1989 has been associated with controversies and concerns, which remain after almost two decades of investigation and practical experience. When to start, how to use, what targets to achieve, and what outcomes to assess are but some of the questions that persist in the management of anemia in dialysis patients. The debate expanded when the use of erythropoietin was extended into the treatment of anemia in earlier stages of chronic kidney disease (CKD), before the need for dialysis. The publication of clinical practice guidelines on the management of anemia in CKD by several organizations has been instrumental in reducing the wide variations in practice that followed the initial use of erythropoietin. The gaps in knowledge identified in these guidelines have provided a basis for much of the research that has been published on the subject since that time.

An upper limit of the targeted hemoglobin level was a component of the initial guidelines[1] because of the Normal Hematocrit Cardiac Trial published in 1998,[2] which suggested that attempts to normalize hematocrit in hemodialysis patients was associated with harm. The upper limit for targeted hemoglobin was liberalized in the course of updating the original guidelines because of observational studies showing a reduction in hospitalization, morbidity, and mortality at higher achieved levels of hemoglobin.[3–5] Nevertheless, concerns remained because of the limited available data on the effectiveness, efficacy, and safety of the recommended targets, especially when complete correction of anemia did not lead to an associated improvement in the left ventricular mass.[6] These concerns were magnified when two large clinical trials in patients with CKD stages 3 and 4 (CHOIR and CREATE) were published in November 2006 showing no benefit in one (CREATE) and harm in the other

(CHOIR) with respect to cardiovascular outcomes in subjects randomized to a higher target hemoglobin level.[7,8] The subsequent debate extended beyond the medical literature, entailed regulatory agencies, and challenged the existing guidelines that were, in fact, the catalysts that prompted some of the very clinical trials that initiated the controversy.[9]

To address these issues, Kidney Disease Outcomes Quality Initiative (KDOQI), which had released its updated anemia guidelines in 2006 prior to the new data being published, reconvened a workgroup to review these and other newer studies. After thorough assessment of all the available evidence, including the recently published trials, KDOQI published revised recommendations for the target hemoglobin level in CKD patients in September 2007.[10]

At the same time, KDIGO convened a meeting in October 2007 to review anemia management in CKD patients and to develop recommendations for future guidelines in this field. This report presents the deliberations and recommendations of the meeting. It has been reviewed by the conference participants and adopted as a position statement by the KDIGO Board of Directors.

CONFERENCE PROCEEDINGS

The agenda, scope of work, papers, and documents distributed at the meeting, and other pertinent material mentioned in this report are posted on the KDIGO website (http://www.kdigo.org). The scope of work acknowledged the importance of correcting anemia and emphasized the importance for the international nephrology community to come together to evaluate emerging safety and efficacy concerns in anemia correction, identify gaps in knowledge, and adopt a common approach to future anemia guidelines that would avoid duplication of efforts in deriving recommendations from a limited evidence base. In preparation for the meeting, the conference co-chairs (Francesco Locatelli and Allen Nissenson) worked together with the KDIGO co-chairs (Norbert Lameire, Kai-Uwe Eckardt, and Garabed Eknoyan) to define the issues to be addressed; to evaluate on-going clinical trials in the treatment of anemia in CKD, cancer, and cardiovascular disease; and to compile a participant list. Invited participants included the leadership of five principal guideline development organizations (Caring for Australians with Renal Impairment (CARI), Canadian Society of Nephrology (CSN), European Best Practice Guidelines (EBPG), KDOQI, and United Kingdom Renal Association (UK-RA)); their experts in the development and implementation of guidelines, methodologists, specialists in quality-of-life (QOL) measurement in CKD, and other investigators in the field.

The meeting started with a plenary session during which the presenters provided a comparison of the methodology and recommended hemoglobin target levels of the five principal guidelines published in English; the evidence base of the recommendations of the KDOQI 2007 update; an overview of the status of new erythropoiesis-stimulating agents (ESA) and iron supplements; the design and timeline of the ongoing Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) study,[11] the merits, and limitations of QOL studies in CKD; and the need for the coordination of future guidelines on anemia in CKD. The participants then met in two breakout groups to address the topics covered, and a number of specific questions were designed to consider the existing knowledge, how it can be used, and the direction of future research. The recommendations of each of the breakout groups were then presented by their respective leaders and rapporteurs (Rowan Walker, David Wheeler, Brendan Barrett, Francesco Locatelli, and Allen Nissenson) to the entire group for discussion and refinement. What follows is a summary of the deliberations and specific recommendation made.

FRAMING THE ISSUES

There was a widespread agreement on the following issues and gaps in knowledge that deserve to be examined in future studies:

Anemia

(1) The current evidence, based on mortality data, for hemoglobin target levels intentionally aimed with ESA treatment in CKD patients treated indicates that
   - levels of >13 g per 100 ml can be associated with harm,
   - levels of 9.5–11.5 g per 100 ml are associated with better outcomes compared with >13 g per 100 ml
   - for levels between 11.5 and 13 g per 100 ml, there is no evidence at this time for harm or benefit compared with higher or lower levels.

(2) The relationship of the dose of ESA used and outcomes has not been examined adequately. Associations between the need for higher doses of ESA and poor outcomes could be surrogates for underlying comorbidities or toxicity. Outcome studies of ESAs have heretofore based their interventional strategies on hemoglobin levels only, wherein the levels of hemoglobin achieved is equated with efficacy. There is a need to broaden the primary end points of clinical trials. Studies examining a given dose of ESA, as opposed to, or in combination with, that of an achieved hemoglobin target, are needed to evaluate resistance, nonresponsiveness, and ESA toxicity.

(3) The mechanisms of resistance to anemia correction remain poorly defined. A consistent definition of ESA resistance is crucial for future research. Proposed resistance indices need evaluation and validation. Markers that can predict nonresponsiveness should be explored.

(4) QOL studies published heretofore are of varying quality and often inconclusive, but suggest some improvement following the correction of anemia with ESAs. The science of QOL assessment has evolved and more reliable methods of determining patient-related outcomes and functional status are now available. There is a need for more robust randomized clinical trials where appropriate QOL domains are the primary end points at different levels of hemoglobin.

(5) There is a considerable heterogeneity in the patient data used in meta-analyses, which cover the spectrum of patients with CKD. Differences in the outcomes of anemia treatment between dialysis patients and those in CKD stages 1–5 are not clear. The impact of comorbidities and intercurrent illnesses on targets has not been well examined. Individual patient data meta-analysis should be performed using existing databases to further explore potential sources of heterogeneity.
(6) In addition to the analysis of available databases, randomized clinical trials should be performed to enhance our understanding of the profile of high-risk patients, exploring the impact of comorbidities, treatment modalities, and intercurrent illnesses on outcomes at different target hemoglobin levels.
(7) A better understanding of hemoglobin kinetics in the ESA correction of anemia is required. Variations in hemoglobin levels (hemoglobin cycling), what they mean, and their clinical implications, if any, deserve further elucidation.

Iron supplementation

(1) The tools for measuring iron status are crude.
(2) Recommended iron levels are directed at optimizing ESA use and target hemoglobin levels. The potential toxicity of iron remains an issue that should be investigated and elucidated.
(3) There is lack of information comparing the efficacy and safety of various iron preparations, regimens, and routes of administration.

Anemia guidelines

(1) Published guidelines largely ignore transfusion reduction as a primary reason for ESA use.
(2) Guidelines need to provide clear descriptions not only of what is known but also of the gaps in current knowledge.
(3) The evidence tables in published guideline documents would benefit from explanatory notes interpreting the data presented to general users of the guidelines.
(4) Guidelines should address whether recommended targets need to be followed in individuals who are acutely ill or have chronic inflammation.
(5) Guidelines should comment on the data generated from studies in cancer and cardiac patients and their implications for the use of ESAs in CKD patients.
(6) The KDOQI 2006 update and its subsequent 2007 modification are comprehensive documents, which represent a good summary of the current evidence and provide sound recommendations.

CONCLUSION AND RECOMMENDATIONS

In the closing plenary session, there was considerable discussion on how the KDOQI guidelines could be used in the context of other available guidelines. There was a general agreement that there is insufficient new data to justify a revision of these guidelines at the present time.[12] On the other hand, despite the international composition of the KDOQI anemia guideline development workgroup, concern was expressed about the challenge they present from a global perspective, bearing in mind regional policies, resources, and sensitivities. It was pointed out that there is a distinction between the factual evidence report of guidelines and its interpretation in the consensus-developed statement of recommendations made. As with any other guidelines, regional resources and policies vary resulting in different levels of recommendation arising from the same scientific evidence. The stated concerns notwithstanding, it was agreed that there is a clear need to save resources and avoid duplication in the next iteration of guidelines, which should be developed as a cooperative global undertaking. Although the level of comfort and acceptance of such a project needs to be nurtured, any obstacles that exist to producing a common global guideline can be overcome. It is recommended that

1. The next clinical practice guidelines on anemia in CKD, including the new evidence review process, would be a coordinated effort undertaken by KDIGO.
2. Based on anticipated results from key on-going studies, it is reasonable to plan for a start-up date no earlier than 2009, with an anticipated completion date of 2011.
3. Adoption and implementation of the guidelines will remain a regional decision based on the evidence tables of the new KDIGO guidelines. Given the differences in health-care systems and resource availability, the prioritization and strength of individual recommendations made would have to be undertaken at the regional level, wherever deemed necessary.

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