Systematic Review of Controlled Trials on Erythropoietin to Support Evidence-Based Guidelines

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To support evidence-based clinical guidelines on erythropoietin use for anemia in oncology, we conducted systematic reviews of controlled trials on four patient groups. These were patients with treatment-related anemia; patients with disease-related anemia; patients transplanted with allogeneic hematopoietic stem cells; and those transplanted with autologous hematopoietic stem cells.

In 1997, the Agency for Health Care Policy and Research, now known as the Agency for Healthcare Research and Quality (AHRQ), launched an initiative to promote evidence-based practice in everyday care by establishing 12 Evidence-based Practice Centers. AHRQ establishes contracts with the Evidence-based Practice Centers to develop evidence reports and technology assessments on clinical topics that are common, expensive, and/or significant for the Medicare and Medicaid populations. Through this program, AHRQ partners with private and public organizations to improve the quality, effectiveness, and appropriateness of clinical care by facilitating the translation of research evidence into clinical practice.

Approach to Systematic Reviews

Program Overview

In 1998, the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) jointly nominated the topic "Uses of Erythropoietin in Oncology" to AHRQ for an Evidence-based Practice Center systematic review and evidence report. A panel appointed jointly by ASH and ASCO intended to use the resulting evidence report to support development of a clinical guideline for dissemination to their members. AHRQ contracted with the Blue Cross and Blue Shield Association (BCBSA) Technology Evaluation Center Evidence-based Practice Center to conduct the systematic review and evidence report on erythropoietin.

Evidence-based Practice Centers develop evidence reports and technology assessments based on rigorous, comprehensive syntheses and analyses of relevant scientific literature, emphasizing explicit and detailed documentation of methods, rationale, and assumptions. These scientific syntheses may include meta-analyses and cost analyses. Each Evidence-based Practice Center collaborates with other medical and research organizations so that a broad range of experts is included in the development process. More detailed information on the Evidence-based Practice Centers program, the topic nomination process, and the list of centers is available at http://www.ahrq.gov/clinic/epcix.htm.[1] Executive summaries and full copies of completed reports (with bibliographies and evidence tables) are available at the same URL for viewing or complimentary downloading. Complimentary single, printed copies also may be obtained from the AHRQ Publications Clearinghouse (1-800-358-9295).

Systematic Review Methods

Protocols for systematic review are prospectively designed to define study objectives and key questions; search strategy; patient populations of interest; study selection criteria and methods to determine study eligibility; outcomes of interest; data elements to be abstracted and abstraction methods; and methods to assess study quality. Usually, two independent reviewers complete each step of the protocol. Reviewers individually evaluate studies against selection criteria, abstract data separately, and compare their results after each step. Disagreements are generally resolved by consensus but may require resolution by a third reviewer.

A technical advisory group provides ongoing guidance on all phases of each Evidence-based Practice Centers’ review. Six technical advisors participated in the evidence report on use of erythropoietin in oncology patients. ASCO and ASCO each appointed two of the six advisors (including the guideline
Evidence-based Practice Centers reviews begin with a comprehensive literature search that attempts to identify all publications of relevant controlled trials. The search strategy for the review on erythropoietin is described briefly in the Executive Summary posted on the AHRQ web site[1] and more completely in the full evidence report.[2] The Medline, Cancerlit, and Embase databases, last searched in December 1998, yielded 2,915 references. We identified 28 additional reports by supplementary searches (eg, Current Contents, bibliographies from manufacturers) through October 30, 1999, for a total yield of 2,943 references.

Next, studies are selected for data abstraction using criteria specified in the protocol. The primary study selection criteria for the erythropoietin review required that studies be designed as controlled trials comparing the outcomes of managing anemia with and without erythropoietin in a patient population relevant to one of four clinical settings. These were (1) anemia due primarily to cancer therapy; (2) anemia due primarily to a malignancy; (3) high-dose myeloablative therapy followed by an allogeneic transplant of hematopoietic stem cells from peripheral blood or bone marrow; and (4) high-dose myeloablative therapy followed by an autologous transplant of hematopoietic stem cells. We defined the setting as anemia primarily due to cancer therapy if trials limited enrollment to patients undergoing concurrent chemotherapy or radiation therapy with conventional nonmyeloablative doses. We defined the setting as anemia primarily due to malignancy if some enrolled patients did not receive concurrent chemotherapy or radiation therapy while on study.[2] Trials were excluded if there were < 10 similarly treated evaluable patients in each arm.

In the available trials, erythropoietin treatment (with transfusion used as necessary) was always compared with red blood cell (RBC) transfusion alone; no trials compared erythropoietin to any other alternative. All randomized controlled trials relevant to any of the four clinical settings were included. Studies that used nonrandomized concurrent or historical controls were included if the reviewers could determine that similar patients were included in the treatment and control groups. Nonrandomized trials were considered to be of lesser quality than randomized controlled trials. Outcomes of interest included

- Magnitude of change in hemoglobin (Hgb) levels.
- Percentage of patients who met criteria for a hematologic response as defined in each study’s protocol.
- Percentage of patients who were transfused.
- Number of RBC units transfused per patient normalized to a 4-week period.
- Quality of life.
- Symptoms of anemia (besides fatigue or other components measured by quality-of-life questionnaires).
- Adverse effects of treatment.

The systematic review addressed the following key questions separately for each clinical setting:

1. **Effects of Erythropoietin Treatment** What were the relative effects on outcomes of managing anemia with erythropoietin compared with transfusion alone? In settings other than stem-cell transplants, what were the relative effects of erythropoietin treatment when different Hgb thresholds were used to initiate erythropoietin treatment?

2. **Variations in Erythropoietin Regimens** In the included studies, did variations in the erythropoietin treatment regimen (such as dose, frequency, duration, route) affect the outcomes of treatment? Were these variations likely to confound interpretation of the evidence on the relative effects of erythropoietin treatment according to the alternative Hgb thresholds for initiating treatment?

3. **Identification of Patient Response** Were there populations or subgroups of patients more or less likely to benefit from erythropoietin treatment? Were there laboratory measurements that either predicted or permitted early identification of patients whose anemia responded to erythropoietin?

4. **Data on Adverse Effects** What were the incidence and severity of adverse effects associated with the use of erythropoietin and how did these compare with the adverse effects of transfusion? Data abstraction for adverse events also was limited to controlled trials so that effects of erythropoietin could be distinguished from effects of disease progression or concurrent therapies for the underlying malignancies.

To supplement the systematic review, we conducted a literature-based meta-analysis of the effect of erythropoietin on the odds of transfusion for patients with anemia or at risk of anemia due primarily...
to cancer therapy. A random effects model was used to calculate the combined odds ratio of transfusion for the 12 randomized controlled trials that reported numbers or percentages of patients transfused, with or without erythropoietin administered subcutaneously, for treatment-related anemia. The odds ratio expresses the relative likelihood that erythropoietin-treated patients will be transfused compared with the likelihood for controls. Published data were insufficient for literature-based meta-analysis of other outcomes, or of odds of transfusion in other clinical settings. Sensitivity analysis compared results of higher-quality trials to those of lesser-quality trials. A trial was classified as higher quality when it was randomized and double-blinded and met our criteria concerning limits on the number of subjects excluded from the analysis of results. We required that < 10% of subjects within each study arm were excluded from the analysis and that the ratio of exclusions from each arm was less than 2:1; or, alternatively, that results were reported as an intention-to-treat analysis.

**External Review**

AHRQ requires that Evidence-based Practice Center reports undergo extensive review by external experts and representatives of stakeholder organizations. Early in each project, these individuals review and provide input to modify the study protocol. Later, they review and comment on the report’s initial draft. However, each Evidence-based Practice Center has ultimate responsibility for the final draft of its reports, subject to AHRQ review.

For the erythropoietin report,[2] the BCBSA Technology Evaluation Center Medical Advisory Panel, which includes nationally recognized experts in technology assessment and hematology/oncology, reviewed a preliminary analysis of the evidence base. Additionally, 20 external reviewers critiqued the study protocol and draft report, and revisions were made based on their comments. Eight reviewers were invited by Technology Evaluation Center based on their expertise in medical oncology, hematology, transfusion medicine, quality-of-life and systematic review methodology. One reviewer directed another AHRQ Evidence-based Practice Center and is a medical oncologist. Ten reviewers were appointed by professional organizations other than ASCO or ASH and by patient advocacy groups. These reviewers included clinical and research specialists involved in the treatment of cancer and/or management of cancer-related anemia and patient advocacy representatives. One external reviewer was from the technical staff of Ortho Biotech, Inc. Lists of the Technology Evaluation Center Medical Advisory Panel members, external reviewers, and technical advisors are included in the evidence report’s appendices.[2]

**Erythropoietin for Anemia Primarily Due to Cancer Therapy**

**Erythropoietin vs Transfusion**

The evidence review is based on data abstraction and analysis of 22 controlled trials with a total enrollment of 1,927 patients.[3-24] All trials compared the outcomes of using erythropoietin to manage anemia in patients undergoing therapy for a malignancy with the outcomes of RBC transfusion alone. As shown in **Table 1**, 18 trials with 1,698 enrolled patients (88%) were randomized, [3-20] and 7 of these (853 patients; 44%) were placebo-controlled and double-blind.[3-9] For all 22 trials, the number of patients reported as evaluable is 1,838, which is 95% of all enrolled patients. We classified the 22 trials into three categories defined by the study patients’ mean Hgb at enrollment: Hgb ≤ 10 g/dL [3-7,9,11,15,16,23]; Hgb > 10 but < 12 g/dL[8,10,12,17,21,22,24]; and Hgb ≥ 12 g/dL[13,14,18-20]. No trials directly compared the outcomes of initiating erythropoietin treatment at different Hgb thresholds.

The systematic review found adequate and consistent evidence that erythropoietin increased Hgb levels and percentage of patients demonstrating hematologic response, when compared with controls managed by transfusion alone (**Table 2**). This was true for pediatric patients as well as adults.

Most trials (17 of 22) reported the number or percentage of patients transfused (**Tables 1 and 3**), although many reported that differences between arms were not statistically significant, and a few did not test for the statistical significance of differences they reported. Just above half the trials (12 of 22) reported the number of RBC units transfused per patient (**Tables 1 and 3**). No trials reported effects of erythropoietin use on symptoms of anemia other than fatigue (not shown).

For all randomized studies that gave erythropoietin subcutaneously,[3-7,10-12,14,16,19,20] meta-analysis showed that erythropoietin reduced the odds of transfusion by a factor of 0.38 compared with controls not given erythropoietin (**Table 4; Figure 1**). This indicated that the likelihood of transfusion for erythropoietin-treated patients was 38% of the likelihood for controls. The overall number needed to treat (NNT) calculated for this group of studies was 4.4 (95%...
confident interval [CI] = 3.6-6.1), which suggested four or five patients must be treated with erythropoietin to spare one patient from transfusion. Sensitivity analysis found a smaller magnitude of risk reduction for higher-quality studies,[3-7] which were double-blinded (Figure 2; Table 4). For higher-quality studies, the calculated NNT was 5.2 (95% CI = 3.8-8.4), and for lower-quality studies,[10-12,14,16,19,20] the calculated NNT was 2.6 (95% CI = 2.1-3.8). Thus, higher-quality studies predicted one patient would avoid transfusion for every five to six patients treated with erythropoietin, while the lesser-quality studies predicted one for every two to three patients treated. There was evidence that in unblinded studies physicians may have been more aggressive in transfusing patients in the control arm, thus overestimating the observed effect of erythropoietin.[14]

**QOL Outcomes**

The strongest evidence for an effect of erythropoietin on quality-of-life outcomes (Table 5) was a randomized, double-blinded, placebo-controlled trial available only as an abstract but later published in full.[7] In a patient population with mean baseline Hgb level ≤ 10 g/dL, investigators reported statistically significant differences in score changes that favored the erythropoietin-treated arm for three questions that used visual analog scales (number of patients evaluable = 335) and for the Functional Assessment of Cancer Treatment-Anemia (FACT-An) (number of patients evaluable = 290). The study also reported statistically significant positive correlations between changes in Hgb levels and changes in quality-of-life scores. However, key methodologic features of administering the quality-of-life instruments[2] were not described. Additionally, the minimum changes in quality-of-life scores considered clinically significant were not defined prospectively or in the discussion of results. Furthermore, this trial did not actually compare the quality-of-life effects of initiating erythropoietin treatment at alternative thresholds of baseline Hgb, nor did the analysis stratify patients by different Hgb levels at entry. Eight other published studies,[3,4,6,13,14,19,20,23] which included a total of 516 evaluable patients, did not provide consistent evidence that erythropoietin improved quality-of-life outcomes. As shown in Table 6, two of these reported only within-arm comparisons of initial scores to final scores, but did not compare the experimental and control arms to each other.[3,14]

**Relative Effects at Different Hgb Thresholds**

The most robust evidence that erythropoietin improves transfusion outcomes for patients undergoing therapy for malignancy compared with transfusions alone came from trials in patient groups with baseline Hgb ≤ 10 g/dL.[3-7,9,11,15,16,23] Transfusion outcomes did not appear to be superior in trials where erythropoietin treatment was initiated in groups of patients who have mean Hgb > 10 g/dL compared with trials where mean Hgb was ≤ 10 g/dL (Table 3). Among trials in adult patients with a baseline Hgb ≤ 10 g/dL, the range of differences between erythropoietin and control arms for the percentage of patients transfused was 9% to 45%. [3-7,11,15] For a baseline level of Hgb > 10 but < 12 g/dL, the range was 7% to 47%[8,10,12,17,21,22,24]; and 7% to 39% for a baseline level of Hgb ≥ 12 g/dL.[13,14,18-20] However, these ranges are wide, and it is uncertain whether the three groups of studies compared patient populations that were similar except for baseline Hgb. The available evidence was inadequate to determine whether outcomes of erythropoietin treatment were superior when treatment was initiated in groups who have mean Hgb > 10 g/dL, compared with groups where mean Hgb is ≤ 10 g/dL. Randomized controlled trials, double-blinded and adequately powered, are necessary to compare the outcomes of erythropoietin treatment initiated at various Hgb thresholds. Inferences from indirect comparison of the results of the available trials cannot resolve this question. It is possible that adequately powered comparative trials might show fewer transfusions when erythropoietin treatment starts at higher Hgb levels than when it starts near 10 g/dL. However, examining the evidence we reviewed suggests two reasons why this is unlikely. First, patients with entry-level Hgb below the mean may have accounted for most of the transfusions among erythropoietin-treated patients in trials where baseline Hgb was ≤ 10 g/dL. Thus, the greatest yield for reducing the number of patients transfused in this population might come from initiating erythropoietin before the Hgb level falls substantially below 10 g/dL, rather than by initiating erythropoietin treatment at a level substantially above 10 g/dL. Second, in all trials, patients who were unresponsive to erythropoietin may have accounted for a substantial proportion of patients transfused. Initiating erythropoietin treatment at a higher Hgb level is not expected to reduce transfusions in this subgroup of patients.

**Effects of Different Methods for Administering Erythropoietin**

The meta-analysis examined whether the characteristics of erythropoietin administration (dosing
regimen, treatment duration, dose range) had an effect on the estimate of the summary odds ratio for transfusion. Only erythropoietin dose appeared to have an independent effect on transfusion outcomes, but this was potentially confounded by study quality. However, the results of two randomized controlled trials that directly compared lower and higher doses of erythropoietin (450 vs 900 U/kg/wk) did not demonstrate that the higher dose was superior in preventing transfusions.[12,14]

**Effects of Patient Characteristics**

- **Age** Erythropoietin was effective in preventing transfusion in pediatric patients.[16,23] No studies reported outcomes stratified specifically for geriatric patients, but adults up to age 90 were included in some trials.[3,4,7]
- **Malignant Disease** There was evidence that erythropoietin produced hematologic responses and probably reduced transfusions in patients with nonmyeloid hematologic malignancies[7,15] to a similar degree as in patients with tumors of solid organs or tissues.
- **Radiotherapy** Although erythropoietin increased Hgb levels for patients managed with radiotherapy alone, mean Hgb levels of control patients did not decrease from baseline values.[13,17,22] The radiotherapy regimens utilized apparently did not contribute to or exacerbate pre-existing mild anemia.
- **Platinum Regimens** The evidence demonstrated benefit from erythropoietin for patients given chemotherapy regimens that included cisplatin or carboplatin, as well as regimens that did not include either of the platinum drugs.[2] (See the full evidence report[2] for citations.)
- **Predictors of Response** The 22 trials included in this evidence base reported no significant predictors of response to erythropoietin therapy.[2] In particular, neither baseline serum erythropoietin nor the ratio of observed to predicted serum erythropoietin levels (O/P ratio) predicted response in any analysis.

**Adverse Effects Associated With Erythropoietin Use**

Limited evidence on adverse events was available from the studies included in this review, but the frequencies of those reported did not appear to differ markedly between erythropoietin-treated patients and controls.[2] The only statistically significant difference was a greater frequency of fatigue reported by patients in the control arms.

**Anemia Due Primarily to Malignant Disease**

The literature search identified six controlled trials (Table 7), all randomized, with a total enrollment of 693 patients that met inclusion criteria for this systematic review.[25-30] Three trials were placebo-controlled and double-blind (n = 332; 48%).[25-27] Of the 693 patients enrolled, 648 (93.5%) were reported as evaluable. Patients in this evidence base had diagnoses known to have a high occurrence of anemia of malignancy (multiple myeloma, non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, and myelodysplastic syndromes). With the exception of one trial in patients with myelodysplastic syndromes,[25] the preponderance of patients in these trials received concurrent therapy for their malignancy.

**Erythropoietin vs Transfusion**

There was consistent evidence that erythropoietin increased Hgb levels and percent of patients demonstrating hematologic response in patients with anemia of malignancy (Table 7). The evidence on transfusion outcomes was sparse, but suggested a favorable effect of erythropoietin treatment. The only report on measurements of quality of life was an abstract that did not provide sufficient detail for interpretation of the results.[27] All patients included in these studies had baseline hemoglobin £ 10 g/dL. The evidence did not address alternative thresholds for initiating erythropoietin treatment in patients with anemia of malignancy.

**Effects of Different Methods for Administering Erythropoietin**

The studies suggested that starting doses in the 200 to 450 U/kg/wk range were adequate to achieve hematologic response. However, the only study of patients with myelodysplastic syndrome used a much higher dose, 1,050 U/kg/wk, yet obtained a smaller increase in response rate.[25] The distinct mechanism of anemia in this clonal disorder probably contributed to the reduced response rate.

**Effects of Patient Characteristics**

- **Malignant Disease** A statistically significant hematologic response in the erythropoietin arm was reported for all hematologic malignancies included in this review. However, the
limited evidence available suggested that hematologic response rates were lower for patients with myelodysplastic syndrome.

- **Age** All studies were of adults. There were no studies of pediatric patients or that separately reported on geriatric patients.

- **Prior Transfusion** Erythropoietin increased hematologic responses or Hgb levels for patients with either multiple myeloma or non-Hodgkin’s lymphoma, irrespective of history of prior transfusion.[28-30] A single study of myelodysplastic syndrome patients reported that erythropoietin increased hematologic responses for patients without previous history of transfusion, but not for those previously transfused.[25] History of prior transfusion, however, may be associated with other characteristics, such as duration and progression of disease (which may have affected erythropoiesis in myelodysplastic syndrome patients).

- **Predictors of Response** This group of studies did not provide sufficient evidence to draw conclusions on predictors of response. Only the serum concentration of endogenous erythropoietin at baseline[25,30] and the ratio of observed to expected concentrations of serum erythropoietin[28,30] were reported as significant predictors of response in at least two trials.

### Adverse Effects
There was a statistically significant increase in hypertension (10% vs 1%; P = .011) and a nonsignificant increase in thromboembolic events (3% vs 0%; P = .55) among those treated with erythropoietin. The reported frequency of adverse events other than hypertension and thromboembolic events did not appear to differ between erythropoietin-treated patients and controls.

### Anemia Resulting From Marrow Ablation and Allogeneic Stem-Cell Rescue

#### Erythropoietin vs Transfusion
The evidence concerning the use of erythropoietin after high-dose chemotherapy and allogeneic stem-cell transplantation was derived from seven controlled studies (total enrollment: 493) of patients with malignancies that are representative of those undergoing marrow-derived allogeneic stem-cell transplantation in clinical practice.[31-37] Of the seven controlled trials, all but two[31-35] were randomized (total enrollment in randomized studies: 400); nonrandomized trials compared erythropoietin-treated patients with historical controls.[36,37] The largest study enrolled and evaluated 215 patients[31]; all other studies enrolled fewer than 100 patients. Outcomes reported from these seven trials are summarized in Table 8, with the studies listed in order of increasing erythropoietin dose.

These studies compared the outcomes of transfusion of red blood cells initiated at a predefined threshold with the outcomes of erythropoietin treatment supplemented with transfusion of red blood cells when necessary. One study exclusively enrolled pediatric patients.[37] The enrolled patients had a variety of hematologic tumors. All of the studies used marrow as the stem-cell source, and all studies administered erythropoietin intravenously.

In four of five trials reporting this outcome, erythropoietin resulted in a statistically significant decrease in the time to RBC engraftment (see Table 8), as indicated by achievement of a predetermined Hgb level independent of transfusion support.[31-33,36] The range of reduction reported was 1 to 2 weeks. Reticulocyte measures, which tend to predict RBC engraftment, also suggested more rapid engraftment with erythropoietin administration.[31,33-37]

Outcomes for day of last transfusion were related to and correlated with RBC engraftment by Hgb level results, with statistically significant results favoring the erythropoietin-treated study arm.[31,32,36]

Erythropoietin administration is unlikely to spare anyone from transfusion, as recipients of allogeneic stem-cell transplantation are uniformly anemic following the procedure and response to erythropoietin, whether endogenous or exogenous, is not immediate. The evidence suggested, however that erythropoietin treatment may have decreased the number of RBC units transfused.[32,34,35,37]

Limited evidence suggested that erythropoietin treatment had no significant effect on length of hospital stay.[32,33] This is not surprising, given the number of complications from allogeneic stem-cell transplantation that are unrelated to anemia.

#### Effects of Different Methods for Administering Erythropoietin
Transfusion outcomes appeared to be associated with the duration of follow-up for reporting and
statistical comparison: Shorter follow-up was more often associated with a significant beneficial effect,[34,35,37] whereas longer follow-up may have been complicated by transfusions for graft-vs-host disease and resulted in nonsignificant outcomes for erythropoietin.[31,33] For both RBC engraftment and RBC transfusion outcomes, results obtained with erythropoietin dose extremes (525 or 3,500 U/kg/wk) [35, 37] did not appear to differ from those obtained with the moderate doses (700-1,050 U/kg/wk) used in most of the studies.

**Effects of Patient Characteristics**

- **Age** Although only one small study (nonrandomized, historical controls) specifically examined the use of erythropoietin in a pediatric population,[37] results were consistent with those obtained in all other studies, which enrolled primarily adult populations. Additionally, significant results were obtained in this study using a dose/kg/wk that was half or less than the doses used in studies of adult patients.

**Adverse Effects**

There did not appear to be significant adverse events associated with erythropoietin treatment in patients receiving allogeneic stem-cell transplants (reporting was sparse however). The available evidence showed no depression of platelet engraftment with erythropoietin treatment.

**Anemia Resulting From Marrow Ablation Prior to Autologous Stem-Cell Rescue**

The literature search and review for studies of erythropoietin use after autologous transplantation identified six controlled trials (total enrollment: 321).[31,37-41] Three of the six trials[31,38,39] were randomized (total enrollment: 169); nonrandomized trials compared erythropoietin-treated patients with historical controls.[37,40,41] Studies ranged in size from 20[38] to 114[31] enrolled patients. All of the studies used marrow as the exclusive source of stem cells except for one[39] in which patients with Hodgkin’s lymphoma were also given peripheral blood stem cells. Nevertheless, it appears that results from these studies can be generalized to patients transplanted with peripheral blood stem cells, the current standard of care. Study outcomes are summarized in Table 9.

**Erythropoietin vs Transfusion**

The evidence did not support a beneficial effect of erythropoietin administration on RBC engraftment, RBC transfusion, or length of hospital stay outcomes. It is particularly noteworthy that two studies,[31,37] that used the same erythropoietin protocol for both allogeneic and autologous stem-cell transplant patients reported several outcomes significantly improved only for allogeneic stem-cell transplant patients.

**Differences in Erythropoietin Administration**

Since the available evidence did not show a clear benefit for erythropoietin treatment, there was no evidence to favor a particular dose, dosing regimen, or treatment duration. Although it is possible that treatment duration was too short in all included studies to significantly improve outcomes, reticulocyte measures (an early indicator of RBC engraftment) did not indicate a probable response.[31,37,39]

**Patient Characteristics**

Erythropoietin did not show a beneficial effect for the entire population of patients treated in these studies. Results among the subpopulations were consistent with overall results, and no subpopulation that derived benefit from erythropoietin treatment could be identified. The lack of response to erythropoietin in patients given marrow stem cells suggests that patients given peripheral blood stem cells would also be unlikely to respond. Preparations of peripheral blood stem cells mobilized with growth factors contain progenitor cells from the erythroid (and other) lineage(s). These progenitors are farther along the maturation pathway to functional end-stage cells, and may be less dependent on erythropoietin than are unstimulated stem cells harvested from the marrow. The time to recovery of red cell counts and correction of anemia thus appears less likely to be shortened by erythropoietin therapy after infusion of peripheral blood stem cells than after infusion of marrow stem cells.

**Adverse Effects**

There did not appear to be significant adverse events associated with erythropoietin treatment in patients receiving autologous stem-cell transplants (reporting was sparse, however). The available evidence showed no depression of platelet engraftment with erythropoietin treatment.

**Future Research**
The most robust evidence that erythropoietin treatment improves outcomes for oncology patients (and its most common oncologic use in the United States) is for those patients concurrently undergoing cancer therapy. Consistent evidence demonstrates that erythropoietin reduces transfusion requirements if treatment is initiated when declining Hgb levels approach 10 g/dL. More limited evidence suggests that erythropoietin also improves quality of life for mildly anemic patients. Inferences from indirect comparisons of results from available trials, however, were unable to resolve the question of an optimal Hgb threshold level for initiating erythropoietin treatment. Inferences from large uncontrolled studies[42-44] that enrolled patients with baseline Hgb levels ≤ 10.5 g/dL also cannot resolve this uncertainty, although they may provide suggestive evidence for a target at which Hgb levels should be maintained in those who are treated. Randomized controlled trials, adequately powered, are needed to directly compare treatment initiated at higher baseline Hgb levels (eg, ≤ 12 g/dL) with treatment delayed until Hgb approaches 10 g/dL. Such direct comparisons can best determine whether earlier initiation of erythropoietin therapy yields greater benefits than delayed treatment, by further reducing transfusion use or improving quality of life. The systematic review also identified common deficiencies in the design and reporting of trials on erythropoietin. In addition to the preponderance of unblinded studies, deficiencies common to this literature included:

- Inadequate statistical power.
- Failure to report on concealment of allocation.
- Failure to consistently report on a common set of clinically relevant outcomes.
- Failure to consistently test and report on statistical significance.
- Failure to account for patients lost to follow-up or excluded from analysis.
- Failure to use intent-to-treat analyses.

Some methodologic deficiencies may result in overestimation of the effects of erythropoietin, and inadequacy of reporting may limit the ability to interpret and generalize results. Future trials should maintain a higher standard of methodologic quality and completeness of reporting. Published trials that reported on quality of life did not follow recognized principles to minimize biases. Consequently, factors other than erythropoietin treatment may have affected outcomes. Future trials should measure effects of erythropoietin on quality of life more rigorously using validated instruments, and by incorporating specific design features related to administration of questionnaires and analysis and interpretation of results.

In nearly all trials, a substantial percentage of patients did not achieve a hematologic response to erythropoietin. Additionally, nonresponding patients may account for much of the transfusion use in the erythropoietin arms of these trials. To achieve the most efficient use of erythropoietin, additional systematic evidence is needed on baseline characteristics that predict responsiveness and on early indicators of response.

The reviewed evidence shows that initial doses of erythropoietin in the range of 300 to 450 U/kg/wk administered subcutaneously are adequate to increase Hgb and reduce the percentage of patients transfused. However, the optimal initial dose within this range has not been determined. Furthermore, within this dose range the team could not discern any difference in response rates between trials that used increasing dose regimens and those that used decreasing dose regimens. To achieve the most efficient use of erythropoietin, comparative trials are needed to establish an optimal initial dose and to determine the optimal dosing regimen.

The team found evidence that patients with myelodysplastic syndromes respond to erythropoietin, although response rates are much lower than in other malignancies, and higher doses of erythropoietin appear to be necessary. To achieve the most efficient use of erythropoietin, additional studies are needed to determine which patients with myelodysplastic syndromes are most likely to respond. Studies are also needed to establish an optimal dose and dosing regimen.

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