Recombinant Human Erythropoietin in Cancer-Related Anemia

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The clinical development of recombinant human erythropoietin (rHuEPO) has had a remarkable impact on the clinical practice of oncology. A decade ago, randomized, placebo-controlled trials in anemic cancer patients demonstrated that rHuEPO resulted in an improvement in hemoglobin and hematocrit, a reduction in transfusion requirements, and improvement in quality-of-life (QOL) endpoints. Based on these trials, recombinant erythropoietin was approved for the treatment of anemia in patients with nonmyeloid malignancies in whom the anemia was caused by the effect of chemotherapy.

Erythropoietin has long been known to be the major regulator of erythropoiesis. In studies more than three decades ago, Finch demonstrated that as hemoglobin levels fall below 12 g/dL, endogenous levels of erythropoietin increase in the plasma.[1] In patients with chronic renal failure and low levels of endogenous erythropoietin, replacement therapy with recombinant human erythropoietin (rHuEPO [Epogen, Procrit]) resulted in normalization of hemoglobin levels.[2] Despite the significant impact erythropoietin therapy had on the renal dialysis patient population, this was felt to be a unique situation related to the lack of erythropoietin production in the setting of renal failure. For anemia due to other causes, it was assumed that recombinant erythropoietin would not be effective, because it was assumed that endogenous erythropoietin responses would occur. However, cancer population studies by Miller and colleagues[3] demonstrated that the endogenous erythropoietin response is blunted in the face of cancer-related anemia. Subsequent studies have suggested that this lack of appropriate erythropoietin response in the setting of cancer may be due to inflammatory cytokines that may also play a role in suppressing erythropoiesis as well as in erythropoietin production.[4]

Erythropoietin Therapy in Cancer Chemotherapy Patients

Pathophysiology

Studies of recombinant erythropoietin demonstrated that the anemia experienced by the cancer chemotherapy patient is multifactorial—partially attributable to the bone marrow suppression of the cancer chemotherapy, partly related to the blunted erythropoietin response and to the suppressive effects of cancer and cytokines on erythropoiesis. Although it was expected that higher doses of erythropoietin would be required, it was remarkable that anemia was ameliorated in most patients with erythropoietin alone, despite this complex multifaceted pathophysiology.

Initial Randomized Trials

The initial randomized, placebo-controlled clinical trials in cancer-related anemia were performed in three separate populations, as outlined in Table 1.[5] One group of patients with cancer-related anemia not associated with chemotherapy received recombinant human erythropoietin at 100 U/kg SC three times weekly vs placebo for an 8-week period. The other two groups of patients with chemotherapy-related anemia received rHuEPO at 150 U/kg SC three times weekly for a 12-week period vs placebo. These two groups were divided into patients receiving cisplatin-based chemotherapy or non-cisplatin-based chemotherapy based on the assumption that cisplatin might be more likely to cause anemia than non-cisplatin-based regimens because of its renal effects. Subsequent trials demonstrated that, in the absence of renal failure, non-cisplatin-containing regimens are equally likely to cause anemia as cisplatin-based therapy and that most myelosuppressive chemotherapy regimens cause similar levels of anemia.[6]

The dose of erythropoietin chosen for the nonchemotherapy group was based on the assumption that a lower dose would be effective in the absence of chemotherapy. While this theory has been proved true, the shorter time-course of therapy did not allow for the differences between the placebo and erythropoietin group to become evident. Therefore, the US Food and Drug Administration (FDA)
limited the initial approval of rHuEPO to patients with non-myeloid malignancies whose anemia was caused by chemotherapy. The primary efficacy criteria in these registration studies were intended to evaluate the change in hematocrit from baseline to final value; to quantify the number of units of transfusions; and to assess patient perception of quality of life (QOL) as measured by the self-administered linear analog scale for the domains of energy, activity, and overall quality of life. The average age of patients in these trials was 61 to 62 years, and their median hematocrit was 28% to 29%. More than 45% of patients had received transfusions in the 2 to 3 months before the study. As expected, patients generally had inappropriately low endogenous erythropoietin levels, with most levels below 100 mU/mL. The results of these trials are shown in Tables 2 and 3, and Figure 1. The nonchemotherapy patients treated for 8 weeks with rHuEPO had a significant improvement in hematocrit (+2.8%) compared with the placebo group (-0.1%). However, the cisplatin and noncisplatin patients (treated for 12 weeks) had an even greater difference, with an improvement of 6% to 6.9% compared with 1.1% to 1.3% for the placebo group. The impact of these changes in hematocrit on transfusion requirements can be seen in Table 3. For the nonchemotherapy group, 26% of both the erythropoietin-treated patients and the placebo patients required transfusions. By contrast, in the combined chemotherapy group, 45.5% of the placebo patients required transfusion vs 27.8% of the erythropoietin-treated patients in the second and third months of the study. These studies demonstrate that the first month of therapy was required to begin to reverse the anemia of treatment and therefore differences in transfusion requirements were not seen until the second and third months. This finding also demonstrates why the nonchemotherapy group was unable to show a transfusion benefit after only 8 weeks of therapy. Figure 1 outlines the changes in QOL measures for self-rated scores of energy level, daily activities, and overall QOL measures from baseline to final evaluation for the erythropoietin-treated vs placebo patients. Utilizing the linear analog scale, patients rate these items on a 100-mm scale. The changes noted by patients displayed greater improvement in quality of life for the erythropoietin-treated patients compared with those receiving placebo for energy level, daily activities, and overall quality of life; only the overall quality of life was shown to be significantly improved for the erythropoietin therapy group (P < .05). This trial also provided an opportunity to carefully assess potential adverse events of recombinant erythropoietin compared with placebo. The reporting of adverse events in both groups was quite similar and reflected the adverse events commonly seen in cancer patients receiving chemotherapy, with only the incidence of diarrhea and edema higher in the rHuEPO group (P < .05). There was a reduction in fatigue from 20% in the placebo group to 15% in the erythropoietin-treated group. Furthermore, there was a statistically significant decrease in dyspnea from 15% in the placebo group to 8% in the erythropoietin group (P < .03). Unlike the renal dialysis population, seizures and hypertension were uncommon in both groups, and not more frequent in the erythropoietin-treated patients, suggesting that these complications may be unique to renal dialysis. 

FDA Approval Guidelines

Based on the results of these placebo-controlled, randomized clinical trials, the FDA approved rHuEPO for the treatment of anemia in patients with non-myeloid malignancies whose anemia was caused by the effects of chemotherapy. The FDA guidelines further clarified that erythropoietin therapy was indicated to decrease the need for transfusions in patients who will receive concomitant chemotherapy for a minimum of 2 months. It was also emphasized that erythropoietin was not indicated in the setting of treatment of anemia caused by other etiologies, such as iron or folate deficiency, hemolysis, or gastrointestinal bleeding. Because the QOL data from these initial registration trials were not as robust as the hematocrit and transfusion data, the use of erythropoietin to improve quality of life was not included as an FDA indication. However, the observation that overall quality of life was improved in the erythropoietin-treated patients led to some of the largest clinical trials ever performed in cancer patients to better define this relationship.

Open-Label, Community-Based Studies

Through the 1990s, three large community studies of rHuEPO were performed in patients with non-myeloid malignancies receiving chemotherapy, as outlined in Table 4.[7-9] All three trials were similar in design, with an open-label, nonrandomized approach. Anemia was a requirement at entry and was defined as hemoglobin < 11.0 g/dL in the latter two studies. The Glaspy et al study utilized
a dose of erythropoietin at 150 U/kg SC three times weekly with an increase to 300 U/kg SC three times weekly if an inadequate response was seen at 8 weeks. In the Demetri et al trial, erythropoietin was given at 10,000 units SC three times weekly with a more aggressive dose escalation to 20,000 units SC three times weekly if the hemoglobin rise was < 1 g/dL at 4 weeks. The Gabrilove et al trial utilized a weekly schedule at 40,000 units SC with an increase to 60,000 units SC weekly if the hemoglobin rise was < 1 g/dL at 4 weeks. In order to account for the impact of disease response and progression during this time, a retrospective tumor response analysis was done in the Glaspy trial, while prospective tumor response analyses were done in the Demetri and Gabrilove studies. Although the absence of a placebo control limits some of the interpretations of these data, the sheer number of patients enrolled in these trials (more than 7,000 patients) provides a robust data set.

Table 5 outlines the outcome variables for these studies. The primary effort in all of these 16-week studies was to look at the impact on hemoglobin, transfusion requirements, and quality of life utilizing the linear analog scale in all three trials. In addition, the Demetri trial utilized the Functional Assessment of Cancer Therapy-Anemia (FACT-An) and the Gabrilove trial used the anemia subscale of the FACT-An, as developed by Cella.[10] The addition of these more detailed QOL questionnaires allowed validation of the linear analog scale results.

Tables 6 and 7 outline the baseline patient characteristics and distribution of tumor types for these three trials. All three studies demonstrate a predominance of females compared to males, with the average age of patients in the 62- to 63-year range. The average hemoglobin at entry on trial was 9.2 to 9.5 g/dL, and 21% to 28% of patients had received prior transfusions. Endogenous erythropoietin levels were again low. Patient characteristics described in Table 7 demonstrate a broad range of tumor types, with 18% of patients having hematologic malignancies and 82% having solid tumors (led by lung, breast, gynecologic, and gastrointestinal cancers).

The results of these studies are seen in Tables 8 and 9. Despite the differences in the dosing of erythropoietin between the three trials, the change from baseline to final hemoglobin levels were quite similar, with all studies achieving a mean change of 1.8 to 2.0 g/dL from baseline to final value (P < .001). However, the differences in dose escalation of erythropoietin did appear to have an impact on reducing transfusion requirements.

In the Glaspy study, the proportion of patients transfused fell from 21.9% (at the beginning of the study) to 10.3% (at the end of the trial). For the Demetri study (with a more aggressive dose escalation of erythropoietin at 4 weeks), the proportion of patients requiring transfusion fell from 28.5% to 5.3%. The Gabrilove study (using a once-a-week dose at 40,000 units with an escalation to 60,000 units in 1 month for patients with a suboptimal response) also demonstrated a similar reduction in transfusion requirements.

### QOL End Points

This large database clearly validated the results of the initial US registration trial in terms of improving hemoglobin and reducing transfusion requirements, but, perhaps even more importantly, allowed careful analysis of QOL parameters, as outlined in Table 10. In all three studies, the mean change in the linear analog score significantly increased compared to baseline in all parameters, with an average improvement of more than 10 mm, which is believed to be a clinically significant magnitude of improvement.

In order to better understand QOL changes from these studies over time, it was important to assess the changes in quality of life and hemoglobin in relationship to tumor response. Table 11 outlines these relationships for the Demetri study, which incorporated careful prospective tumor-response criteria, along with measures of hemoglobin and quality of life, during the conduct of the trial. The patients were categorized as having complete responses, partial responses, stable disease, or progressive disease. As noted, significant improvement in hemoglobin occurred in all four groups of patients, although the magnitude of improvement did correlate with the tumor-response group. There also was a numerically greater improvement in quality of life in the complete-response group compared with other groups. However, even for patients with stable disease, the QOL improvements were quite similar to patients with partial or complete responses. Only the group with progressive disease failed to achieve significant improvements in quality of life. In all of these categories, a stepwise improvement in quality of life could be seen based on changes in hemoglobin levels. This relationship is defined in Figure 2 of the Gabrilove study, using once-weekly dosing of erythropoietin and looking at the domains of energy, activity, and overall quality of life. As noted, for patients who did not achieve an improvement in hemoglobin, there was little or no improvement in...
energy, activity, or overall quality of life, whereas patients who achieved some improvement in hemoglobin (range: 0-2 g/dL) did show improvements in QOL measures. This was further increased in patients who achieve a 2 to 4 g/dL improvement or a > 4 g/dL improvement.

**Target Hemoglobin Levels**

The same relationship between changes in hemoglobin and in QOL scores was seen for all tumor response categories, as outlined in the composite Figure 3. Even in the complete response patients, if the hemoglobin levels did not improve, the QOL scores did not improve. Also, in the stable disease patients (for whom little or no objective tumor response benefit was seen to therapy), if hemoglobin levels improved, QOL benefits were similar to those seen for the partial- and complete-response groups. In the setting of progressive disease the QOL benefit seen with improving hemoglobin levels was blunted, as might be expected in this setting. These data convincingly demonstrate that improved quality of life is associated with increased hemoglobin levels, independent of tumor response.

The Demetri and Gabrilove studies used the Functional Assessment of Cancer Therapy (FACT) scales to further validate these QOL measurements. This scale incorporates 29 general and 20 anemia/fatigue questions that cover the domains of physical, functional, emotional, and social well-being. A high correlation has been demonstrated between the FACT-An and the linear analog scale.[11] The correlation coefficient for the fatigue subscale of FACT-An, the anemia subscale of FACT-An, and the overall FACT-An with the linear analog scale are in the range of 0.7 to 0.72, which demonstrates a very close correlation in biologic systems such as this.

In Figure 4, the percentage change in the FACT-An score for the Gabrilove study compared with the change in hemoglobin level shows the same stepwise improvement noted in Figure 2 using the linear analog scale score. In addition to validating the linear analog scale, the individual questions allowed a more detailed analysis of subgroups. Significant differences were seen in analysis of the response to individual questions by subgroups of patients who had a hemoglobin improvement of < 2 g as compared with those with ≥ 2 g/dL, or in patients who achieved a hemoglobin improvement with a final hemoglobin level < 12 g/dL or ≥ 12 g/dL. Figure 5 demonstrates a representative set of questions and the difference in percent improvement on the FACT-An score based on hemoglobin change.

These studies provide a powerful database that links increasing hemoglobin to improvement in quality of life. It also validates the 2-g/dL increase in hemoglobin levels as an important goal to achieve in patients with significant anemia at baseline. In comparison with the three-times-weekly and once-per-week dosing schedules, the overall responses to erythropoietin as measured by a 2-g/dL improvement in hemoglobin were similar.

In the Demetri trial, 47.1% of patients achieved this hemoglobin improvement at the initial dosing schedule, and 65.8% of patients overall achieved a 2-g/dL improvement in hemoglobin, including those who required a dose escalation. In the Gabrilove study (which involved once-weekly dosing at 40,000 units), 49.2% achieved the 2-g/dL or greater hemoglobin response at the initial dosing, and 68% overall achieved this end point with dose escalation of erythropoietin. Approximately one-third of patients receiving the weekly dose of 40,000 units required dose escalation over the course of the 4-month study.

These three trials concluded that statistically significant improvements in hemoglobin were reported, along with statistically significant reductions in transfusion requirements. In addition, statistically significant improvements in quality of life were seen by the linear analog scale, the FACT-An, and the FACT-An anemia subscale. A direct relationship between hemoglobin and QOL improvements was documented, and improvement in quality of life was linked to increased hemoglobin levels independent of tumor response.

**Meta-analysis Review**

In addition to the initial US randomized placebo-controlled trials and the open-label community-based studies, a large number of additional control clinical trials have been performed and reviewed in a meta-analysis.[12] The details of this meta-analysis will be discussed elsewhere in this supplement. Briefly, this meta-analysis included double-blind, randomized, control trials as well as randomized and unblinded studies. A total of 22 trials were identified, of which 12 could be combined for estimation of odds of transfusion. While these studies varied in their quality, a sensitivity analysis demonstrated that the combined odds ratio for transfusion in erythropoietin-treated patients as compared with controls was 0.45 in the higher-quality studies and 0.14 in the lower-quality studies. Because many of these trials did not include QOL data, this was
insufficient for meta-analysis. It was noted that only studies with mean baseline hemoglobin concentrations of 10 g/dL or less reported statistically significant effects of erythropoietin treatment on quality of life.

The study by Littlewood and colleagues was one of the high-quality trials included in this meta-analysis. This was a randomized placebo-controlled trial conducted in Europe, in which patients received either three-times-weekly rHuEPO or placebo. All patients were required to have anemia secondary to non-platinum-based cancer chemotherapy. A total of 251 patients received erythropoietin and 124 received placebo. Approximately 46% of patients had hematologic malignancies. Of the nonhematologic malignancies, approximately 30% had breast cancer, with a smaller percentage of the other solid tumors represented. The end points of these trials (like the former studies) included hemoglobin response, impact on transfusion, and quality of life. Quality of life was assessed using both the linear analog and the General Functional Assessment of Cancer Therapy (FACT-G) scales. This placebo-controlled study helped to confirm the findings of the initial US registration file, as well as validating the outcomes of the large US community-based studies.

**Results Confirmed**

Figure 6 demonstrates the mean hemoglobin levels for the erythropoietin-treated patients vs the placebo patients over the 28 weeks of the Littlewood trial. As expected, the erythropoietin patients showed significant improvement in hemoglobin that was evident by week 4 of the study. Over the course of the study, the change from baseline to the last value was an average improvement of 2.2 g/dL for the erythropoietin-treated patients vs a 0.5 g/dL improvement for the placebo patients. This difference in hemoglobin improvement was associated with a significant reduction in the proportion of patients transfused. This is consistent with the data from the meta-analysis noted above.

Of particular interest, however, was the QOL data obtained from the Littlewood study. Figure 7 outlines the mean changes in QOL scores from baseline to the end of the study for the domains of energy level, ability to do daily activities, and overall quality of life. As outlined, improvements are noted in all three domains for the erythropoietin-treated patients. By contrast, the QOL measures actually worsened for the patients given placebo, despite maintenance or slight improvement in their hemoglobin levels over the course of the study, as noted in Figure 7. The resultant differences between the groups were highly significant for all three domains: energy ($P = .0007$), ability to do daily activities ($P = .0018$), and overall quality of life ($P = .0048$). These differences were also confirmed by the FACT analysis.

As noted in Figure 8, the erythropoietin-treated patients again showed improvement in their overall QOL scores across the course of the study for the FACT-G, as well as the fatigue and anemia subscales. For the placebo group, a decline in the scores was noted for all three domains. Again, these differences were significant for the FACT-G analysis ($P = .004$), the fatigue subscale ($P = .004$), and the anemia subscale ($P = .0007$).

Another interesting analysis of the Littlewood trial was the comparison between the response rate for patients with solid tumors and hematologic malignancies. As noted in Table 12, 66% to 75% of patients with solid tumors and hematologic malignancies achieved a 2-g/dL improvement in hemoglobin levels. This occurred in 17% to 21% of patients on placebo, suggesting that alterations in chemotherapy dosing or scheduling, or other variables over the course of study, may allow some patients to improve their hemoglobin. Of note, however, the improvement in hemoglobin in these responding placebo patients was not sufficient to reduce the transfusion requirements or improve the quality of life for the group overall. In addition to helping to solidify the correlation between hemoglobin response and improvement in quality of life, the Littlewood trial also reported provocative data on potential impact on survival, which are discussed elsewhere in this publication.

While the meta-analysis of all the trials was unable to make firm conclusions about the impact of erythropoietin treatment on improving quality of life, these data, combined with the original US randomized, placebo-controlled data and the open-label studies, provide strong support for the improvement in quality of life with increased hemoglobin levels for patients treated with erythropoietin.

**New Findings**

The data that assessed the response in terms of the hemoglobin level at time of entry onto the trial were also important. Since studies have not enrolled patients with an average hemoglobin level $> 10$ g/dL (and often not even $> 9$ g/dL), it has not been clear whether patients with less severe anemia would also respond to therapy. As noted in Table 12, the response rate for patients with hemoglobin levels $\leq 10.5$ g/dL was 68.5%. However, for patients who were enrolled with an initial hemoglobin $> 10.5$ g/dL, more than 80% had an improvement in their hemoglobin level $\geq 2$ g/dL with the use of erythropoietic therapy. Of interest, all patients who spontaneously improved their hemoglobin levels
on placebo were in the ≤ 10.5 g/dL group, and none who were in the > 10.5 g/dL group achieved this response. This finding suggests that erythropoietin therapy can be effective for patients with mild anemia, and may even be more effective than for patients with severe anemia.

Relationship Between Hemoglobin and Quality of Life

To further explore the relationship between quality of life and hemoglobin level, an analysis was performed utilizing the database from two of the three large community-based, open-label erythropoietin trials.[7,8] This analysis compared the hemoglobin levels with the overall, patient-reported QOL assessments on the linear analog scale at any point during the trial. The resultant cross-sectional analysis is demonstrated in Figure 9. Although the analysis was limited to time points at which both a hemoglobin measurement and a QOL measurement were made, an average of 800 or more data points are available at each level across most of the range of hemoglobin values. A subsequent analysis was performed to look at these data longitudinally and to try to correct for other confounding variables.[14] Again, because of the large database, those analyses essentially reproduce the results outlined in Figure 9.

The studies show a very similar relationship between an increase in hemoglobin levels and improvement in quality of life. Of particular interest to clinicians, a hemoglobin level between 7 and 10 g/dL correlated with only a slight improvement in quality of life. This is the range for management of patients’ anemia utilizing transfusions before the advent of erythropoietin therapy. Since hemoglobin levels were seldom improved to levels above 10 g/dL, except transiently, it is not surprising that physicians and patients did not note significant differences in QOL endpoints. In contrast, with incremental improvement of hemoglobin levels between 11 and 13 g/dL, substantial changes are noted in the overall QOL assessment. Most patients enrolled in the clinical trials of erythropoietin therapy reached this hemoglobin level, thus resulting in the substantial improvements in quality of life seen in those studies. Of additional interest is the fact that above this hemoglobin range, additional increases in hemoglobin did not result in further substantial improvements in QOL measures.

These data obviously represent an aggregate result; individual patients may differ substantially in the QOL improvements seen at different hemoglobin levels. However, as a group, these data strongly suggest that, from a QOL perspective, an optimal hemoglobin level may range from 12 to 13 g/dL. It is quite interesting that this optimal hemoglobin level is the same level that would have been predicted by Finch’s work demonstrating a rise in endogenous erythropoietin levels when hemoglobin values fall below 12 g/dL. These data would suggest that clinicians need to consider management of even mild anemia if they are to improve patient outcomes from a QOL standpoint. Guidelines that incorporate the results of this incremental analysis need to be developed in order to determine the hemoglobin level at which erythropoietic therapy should be instituted. Furthermore, while this optimal hemoglobin level appears to be quite robust from the quality-of-life measures, an optimal hemoglobin level in terms of tumor response, cognitive function, and other patient outcomes may be quite different, and will await the results of ongoing and future clinical trials.

Conclusions

The randomized trials presented here, as well as the large open-label studies, are supported by an even larger body of evidence supporting the use of erythropoietin in the treatment of anemia in cancer chemotherapy patients. The data clearly demonstrate the ability of erythropoietin to increase hemoglobin levels and reduce transfusion requirements. All of the studies that have adequately assessed quality of life have produced convincing data supporting an improvement in this end point. The improvements in quality of life seen in erythropoietin-treated patients are independent of tumor response. Patients who have a complete or partial response to chemotherapy but no improvement in hemoglobin level do not demonstrate an improvement in quality of life. Furthermore, in the studies of Littlewood et al, placebo recipients who maintained their hemoglobin level during chemotherapy actually showed a decline in QOL outcome. Thus, it would appear that erythropoietin therapy for anemic cancer chemotherapy patients not only prevents worsening of quality of life from the cumulative effects of cancer and its treatment, but also leads to improvement because of higher hemoglobin levels. The chance of response to erythropoietin therapy is approximately 65% to 75% for patients across all of the trials. It appears that patients who have lesser degrees of anemia are more likely to achieve response. Therefore, to minimize the negative impact of chemotherapy on quality of life and to maximize the clinical benefit of erythropoietin
therapy, early intervention at the time of mild anemia should be considered. Ongoing trials evaluating the maintenance of normal hemoglobin levels during chemotherapy and radiation treatment may lead to better understanding of the impact of this treatment on quality of life, cognitive function, and other domains during treatment, as well as the potential impact on tumor response and survival.

References:


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