Erythropoietin and the Management of Anemia in Patients With Lung Cancer

Jeffrey Crawford, MD, and Susan Blackwell, PA-C, MHS

The onset of anemia is a confounding factor that will affect the majority of patients with lung cancer. In an attempt to manage or prevent anemia in this population, three trials have incorporated erythropoietin in the treatment schedules. The results of erythropoietin use for cancer patients with anemia have been encouraging.

Introduction

The majority of the 170,000 patients diagnosed with lung cancer in the United States each year will develop anemia at some point, as a factor of the disease and/or the result of treatment. Management of this complication in the past has been limited to either excluding other causes of anemia in this population or providing red blood cell transfusions for severely anemic patients. Three trials investigating the use of recombinant erythropoietin (epoietin alfa) to treat or prevent anemia in cancer patients, with an emphasis on patients with lung cancer, are reviewed.

The general indications for erythropoietin (EPO) use have expanded greatly over the past decade, from anemia in chronic renal failure dialysis patients initially in 1987, to predialysis and the HIV-related population in 1990, and to chemotherapy-related anemia in 1993. In 1996, recombinant EPO was also approved for anemia due to noncardiac surgery.

Three studies - two completed and one ongoing - are systematically evaluating the effects of EPO on anemia in lung cancer patients. While many questions are yet to be resolved, each of these trials will likely contribute additional information concerning the clinical benefit of EPO in treating or preventing treatment or disease-related anemia.

Registration Trial for Epoietin Alfa

In the original registration trial investigating recombinant EPO in cancer chemotherapy-related anemia, patients were randomized to receive either placebo or epoietin alfa.1,2 Both groups were anemic at presentation. The placebo group continued to be anemic over the 12 weeks of therapy. By contrast, the EPO group had a significant improvement of approximately 6 hematocrit points over this time period. This improvement was seen in both the platinum-based and nonplatinum-based chemotherapy groups who received EPO. In addition, a similar benefit was seen in the anemic nonchemotherapy population receiving EPO, but this did not reach statistical significance, possibly because treatment was continued for only eight weeks. The fact that differences were seen in all three groups is an impressive outcome, given the cross-sectional nature of the study. However, the positive results of this trial were difficult for community oncologists to accept and incorporate in their practices because they represented a change in the standard of care, and physicians were uncertain which patients would be most likely to benefit.

Chemotherapy-Related Anemia: Community-Based Phase IV Trial for Epoietin Alfa

This situation led to the development of a large, community-based, phase IV open-label trial with 2,030 patients evaluated.3 Of the enrolled patients, the lung cancer population was the largest single group of solid-tumor patients (22%). All patients were treated with epoietin alfa at an initial dose of 150 U/kg SQ three times per week over a four-month period.

Endpoints of this broad-based community trial were transfusion requirement, hemoglobin level, and overall quality of life. A total of 1,475 patients (approximately 75% of the population) were evaluable for quality-of-life endpoints, which included energy level, daily activities, and overall quality of life.

Study Results

Patients demonstrated significant improvements in energy level, daily activities, and overall quality of life. Approximately 250 patients in the group of 1,500 did not achieve an improved hemoglobin level. Another 500 achieved an improvement of between 0 to 2 g/dL, and another 500 between 2 to 4 g/dL. More than 200 reached a improvement of greater than 4 g/dL. The majority of the patients in this trial had an improvement of 2 g/dL or more over this four-month period. Improvement in quality-of-life measures increased linearly with the rise in hemoglobin, particularly between 8 to 12 g/dL. There was a continued improvement in the measures above a hemoglobin level of 12 g/dL, but the rate of increase was less. Using these parameters, this study suggests that obtaining and maintaining a hemoglobin level of 12 g/dL or greater is optimal.

The lung cancer subpopulation included 438 patients, with an approximately equal number of men and women. The group consisted of an older population in general (Table 1). The mean hemoglobin level for lung cancer patients was 9 g, and approximately one third had received transfusions. Median pretreatment serum EPO levels were 65. Both carboplatin and cisplatin were commonly included in the treatment programs, with a smaller group receiving a nonplatinum-based chemotherapy (Table 2). Approximately two thirds of the overall patients became transfusion independent. Of the majority who were transfusion-independent at enrollment, only a smaller fraction became transfusion-dependent on treatment.
Mean hemoglobin levels increased steadily from baseline through the four months of therapy, while the proportion of patients requiring transfusion decreased over this time (Fig 1). Because of their smoking history, lung cancer patients are more likely than other types of cancer patients to have comorbid disease such as cardiac disease or chronic obstructive pulmonary disease; thus, they become more symptomatic from lesser degrees of anemia.

<table>
<thead>
<tr>
<th>Mean age (years)</th>
<th>64.5</th>
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<tbody>
<tr>
<td>Mean hemoglobin (g/dL)</td>
<td>9.3</td>
</tr>
<tr>
<td>Patients transfused (%)</td>
<td>25.4</td>
</tr>
<tr>
<td>Mean units transfused/patient/month **</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Endogenous serum erythropoietin level (optional, n=161)

<table>
<thead>
<tr>
<th>Endogenous serum erythropoietin level (optional, n=161)</th>
<th>Mean (mU/mL)</th>
<th>Median (mU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>106</td>
<td>65</td>
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</table>

* Within 4 months prior to study
** Within 1 month prior to study


Table 2. – Lung Cancer Subpopulation: Chemotherapeutic Agents (N=438)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin*</td>
<td>189</td>
</tr>
<tr>
<td>Carboplatin*</td>
<td>109</td>
</tr>
<tr>
<td>Cisplatin/carboplatin</td>
<td>1</td>
</tr>
<tr>
<td>Nonplatinum (total)</td>
<td>87</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>30</td>
</tr>
<tr>
<td>Taxol**</td>
<td>10</td>
</tr>
<tr>
<td>Unspecified</td>
<td>47</td>
</tr>
</tbody>
</table>

* Patients may have received other agents.
** Taxol is a registered trademark of the Bristol-Myers Squibb Co.


Mean hemoglobin levels increased steadily from baseline through the four months of therapy, while the proportion of patients requiring transfusion decreased over this time (Fig 1). Because of their smoking history, lung cancer patients are more likely than other types of cancer patients to have comorbid disease such as cardiac disease or chronic obstructive pulmonary disease; thus, they become more symptomatic from lesser degrees of anemia.
At the time of enrollment, 75% of patients were transfusion-independent. With EPO treatment, 82% of these patients remained transfusion independent over the course of the trial, while 18% developed transfusion dependence. In the transfusion-dependent population, 68% became transfusion independent with EPO treatment.

Adverse experiences from EPO treatment per se were virtually nonexistent. Most of the reported adverse events (eg, disease progression, neutropenia, leukopenia, thrombocytopenia) were likely effects from disease therapy and/or chemotherapy. The study had a high dropout rate, with only approximately 50% of patients completing the study. This rate reflects the nature of the study population and the natural history of lung cancer patients. Disease progression, death, personal reasons, intercurrent illness, and other adverse experiences were responsible for the dropouts.

Quality of Life in Lung Cancer Patients

When quality of life at baseline is compared with that at the termination of this study, the data show a significant improvement in energy level, activity, and overall quality of life for those achieving a 2 g/dL improvement or greater in hemoglobin level. Evaluations were completed for 75% of the population. As noted in Fig 2, the parameters for quality of life improved in a stepwise fashion as a function of increases in hemoglobin level.

Predictors of Overall Response

This and other studies show that an increase in hemoglobin level of greater than 1 g/dL at four weeks (which was the case in approximately half of these patients) predicts for further improvement in anemia. Eighty-one percent will ultimately show at least a 2 g/dL improvement. This finding can be used as a predictor of overall response. If the hemoglobin increase is less than 1 g/dL, only approximately a third eventually demonstrate an improvement of 2 g/dL or more.

Conclusions From the Community-Based Study

The study concludes that an increase in hemoglobin levels in lung cancer patients with anemia can be anticipated in most patients with the use of epoietin alfa, and transfusion requirements were reduced. Improvements were achieved in energy, activity, and overall quality of life, as measured by the linear analogue scale, and the EPO treatment was well tolerated. The following guidelines have been proposed from the data from the overall study for use in the clinical setting of cancer-related anemia.

• Evaluate for another cause of anemia, and if found, treat the cause.
• If no independent cause for anemia is found, start epoietin alfa at a dose of 10,000 U three times per week subcutaneously.
• If patients do not respond, consider increasing the dose.
• If the patient’s hemoglobin rises more than 1 g, continue with epoietin alfa until normal hemoglobin is achieved.
• Decrease or discontinue the dose of epoietin alfa if hemoglobin becomes too high (ie, more than 15 g/dL).

Preemptive Therapy With Epoietin Alfa

In the US registration trial of G-CSF (filgrastim), patients with small-cell lung cancer received either placebo or G-CSF. G-CSF patients received cyclophosphamide, doxorubicin, and etoposide in relatively high doses, followed by either G-CSF support or placebo. Results showed that the number of patients who developed anemia with hemoglobin levels of less than 8 was the same in both arms of the study. Thus, anemia was not an effect of G-CSF per se but resulted from our ability to deliver more chemotherapy since neutropenia was not a limiting factor.

In our experience with this regimen at Duke University, virtually 100% of patients develop anemia and more than 80% require transfusions, with an average of 6 to 8 units of blood during six cycles of therapy. With a goal of preventing anemia, we designed a trial using the same model system in small-cell lung cancer patients receiving cyclophosphamide, doxorubicin, and etoposide with G-CSF support. Enrolled patients were previously untreated and were required to have an hematocrit of greater than 32. The objectives of this trial were to determine if we could prevent anemia in this population and to evaluate the safety of concurrent erythropoietin and G-CSF.

Study Design

Subjects were randomized to receive either erythropoietin or placebo in the first cycle of therapy. The dosing schedule differed from other trials, with 75 µg/dL of epoietin alfa given daily subcutaneously. Although this alteration made direct comparability with the thrice-weekly schedule somewhat difficult, it constituted a similar
The endpoint of this trial was the development of anemia (hematocrit of less than 32) on or after day 1 of cycle 2. Patients on the placebo arm who met the endpoint of the study received open-label epoietin alfa at the same dose and schedule outlined above. This allowed a secondary comparison of a preventive strategy in the epoietin alfa group vs a treatment strategy in the placebo group. In this single institutional trial, the sample size required only 24 patients to determine a 50% difference in the primary endpoint.

Results

In determining if neutropenia worsened as a result of adding epoietin alfa, we found no difference in neutrophil nadir or recovery by the addition of epoietin alfa to G-CSF. We also found no difference in cycle 1 or throughout the treatment in cumulative thrombocytopenia or neutropenia in the group receiving epoietin alfa and filgrastim vs those receiving filgrastim alone.

As an early indicator of red blood cell effect, we measured reticulocyte count weekly, since reticulocytopenia can occur when patients are treated with chemotherapy. Our data showed low absolute reticulocyte counts for the first two weeks in placebo patients. However, the patients on erythropoietin achieved a significant improvement so that by mid-cycle, they were making reticulocytes at greater numbers.

The main endpoint of the study was to determine how many patients who remained on the erythropoietin arm avoided anemia and the need for transfusions. There were a few early failures in cycle 1 in patients with marrow involvement and a few late failures in patients that perhaps were due to cumulative marrow suppression in cycles 5/6. However, the majority of patients using erythropoietin maintained a normal hemoglobin level throughout six cycles of therapy. By contrast, all patients in the placebo arm developed anemia or needed transfusions in the first three cycles of chemotherapy. Although the study was small, it was statistically significant in the final analysis (P < 0.01).

A secondary endpoint was the time to first transfusion. This appeared to be delayed and reduced in the preemptive erythropoietin group compared with the placebo group, but the numbers were too small to reach statistical significance. The patients on the placebo arm who had all crossed over to erythropoietin had an appropriate reticulocytosis, but they remained more anemic than the preemptive erythropoietin group throughout all six treatment cycles. Bone marrow involvement and a baseline hematocrit level of less than 38 were negative predictive factors in terms of response to this dose and schedule of erythropoietin.

Study Conclusions

This study raises several interesting points and suggests that prophylactic use of low-dose, daily erythropoietin can significantly reduce or delay chemotherapy-related anemia compared with placebo in this model system of fairly intensive chemotherapy. Patients who were randomized to placebo received transfusions earlier and remained more anemic throughout the six chemotherapy cycles, despite subsequently being treated with open-label erythropoietin.

If patients with baseline hematocrit levels greater than 38 receive preemptive erythropoietin, our results suggest that anemia or the need for transfusions will likely be avoided. By contrast, patients in this study with marrow involvement who received erythropoietin with this dosing schedule all failed. To determine the optimal dosing schedule of erythropoietin to prevent chemotherapy-related anemia requires a larger study. However, it appears from our study that the earlier one intervenes with erythropoietin in patients at high risk for the development of chemotherapy-related anemia, the more likely a benefit will be gained.

US Multicenter Non-Small-Cell Lung Cancer/Erythropoietin Trial

To further address these issues, a multicenter US trial of epoietin alfa in patients with non-small-cell lung cancer will be initiated in 1998. Investigative arms will be epoietin alpha vs supportive care alone, beginning in the first cycle of chemotherapy, for patients with stage IIIb or IV lung cancer. Patients will be stratified based on hemoglobin levels of either less than or greater than 12 g/dL. Overall, this trial will study the efficacy of erythropoietin as a treatment strategy for anemic lung cancer patients at presentation, as well as a preventive strategy for the nonanemic population. Both groups will be divided into those receiving supportive care alone, with transfusion, or untreated. This trial will not have a crossover to erythropoietin, but patients will be managed with transfusion support as indicated.

A further goal is to investigate whether once-a-week dosing is effective. Most of the usage up to this point has been at 150 U/kg subcutaneously TIW. In noncardiac surgery, a subcutaneous weekly administration at 40,000 U appears to be comparable to 10,000 U three times a week. We learned that the thrice-weekly schedule, while successful, remains a barrier to use of erythropoietin in the community. Thus, all patients randomized to erythropoietin in this trial will receive epoietin alfa at 40,000 U subcutaneously over a week.

The primary endpoint for this trial is quality of life. Additional endpoints include dyspnea, hemoglobin, transfusion requirements, hospitalization, survival, and time to disease progression. The results of this trial should better define and quantitate the clinical benefit of erythropoietin in the lung cancer chemotherapy population.

References


DR BENNETT

I wonder whether a better trial design for the proposed multicenter study would be to offer EPO to both arms, with one group receiving the standard regimen (150...
U/kg three times a week) and the other receiving 40,000 U/wk, with a crossover potential. I think it will be difficult to offer a population of patients the opportunity to participate in a trial in which they may not receive a benefit.

DR CRAWFORD
I agree, but we have the largest database of patients who have received EPO -- 2,000 patients -- that I know of for any cancer other than breast cancer adjuvant therapy. There are another 2,000 patients from another trial. There were good cross-sectional data from the registration trial, but if you look at clinical practice, a minority of cancer patients currently receive EPO when they develop anemia.

DR BENNETT
I think that is changing. The data at our center indicate that increasing numbers of patients are being given EPO. Except in the radiation therapy arena, where they are getting it in a different setting, most patients are getting it after the recognition of severe anemia, but some clinicians are beginning to use EPO to prevent anemia.

DR CRAWFORD
Our new study provides a way to define the population up front, to show the magnitude of difference, and to look at an endpoint other than transfusion requirements. To date, the primary clinical endpoint of most EPO trials has been to reduce transfusion requirements. Making quality of life a primary endpoint instead may provide more important data for clinical efficacy. Also, the trial design, as it is, is simple, and crossovers -- while they sometimes answer additional questions -- always complicate evaluations.

DR SABA
An important aspect of this presentation has been the quality of life data. If there is a definite difference between the transfused patient vs the EPO patient in terms of improvement of fatigue or general well being, then we have to look at other patient populations, too.

DR CRAWFORD
My own bias is that there may be some other effect of erythropoietin. The main issue is that you maintain that hemoglobin of 10 for only a short time with transfusion. Dr Itri has shown a nice linear increase with each gram of hemoglobin, from 8 to 10, 9 to 10, to 11 to 12. And there is just as much, if not more, improvement in that 10-to-12 range as there is from 8 to 10. I think that is something we have not appreciated.

DR ZUCKERMAN
I have tried to make a similar point in the past -- that it costs some extra units of blood to get patients' hemoglobins up several points, but once they are up to your chosen level, it costs no more red cells to keep them between 10 and 12 g of hemoglobin than it does to keep them between 7 and 9 or 6 and 8 g of hemoglobin. And people will do better with that initial investment. Erythropoietin is another (and probably better) way to accomplish that goal. I think this kind of a study is important to answer the question of whether transfusions or EPO should be given to a patient with a hemoglobin of 10 g/dL.

DR MOSCINSKI
We need to separate red cell transfusion from erythropoietin. Much of the argument in the community, as well as a lot of the attitude, has to do with the fact that while red cell transfusions are safe, they have several other complications and comorbid features. Erythropoietin may not necessarily have these.

DR SABA
Another issue is that it takes about two to three weeks for the erythropoietin to take effect. So instead of starting the erythropoietin simultaneously with the chemotherapy, you may start the erythropoietin earlier. In our hematologic malignancy patient population, we realized that if we had started erythropoietin earlier than the chemotherapy, patients could have derived more benefit because all the bone marrow was packed with erythroid precursors.

DR CRAWFORD
I think the idea of the community study was to try to emulate practice. We will administer erythropoietin once a week rather than three times a week to make it easier for practices. I do not know how asking them to start a week before the chemotherapy would translate into practice. It may be something we can look at later, but I think we will start with the first treatment.

DR ZUCKERMAN
I would like to amplify the iron supplementation issue. During the course of our studies in patients with renal failure, we discovered that erythropoietin is an effective way to draw iron out of the iron stores. In fact, another use for erythropoietin was being discussed and considered -- to help to mobilize the iron in hemochromatosis patients.

DR SABA
There are some reports of effective use of EPO in mobilizing iron from patients with hemochromatosis. In our clinic, we have four or five patients with hemochromatosis whom we have treated more effectively with EPO than with anything else.

DR SPIVAK
At this moment, in dialysis units and elsewhere, the issue of how to deal with iron in patients with renal failure who are getting erythropoietin is being analyzed. Dialysis patients lose blood at a tremendous rate -- they are essentially chronic bleeders -- and erythropoietin therapy can really put stress on the system. I would
suggest that it is an entirely different situation you are facing in patients who do not have renal
disease. Patients with cancer, rheumatoid arthritis, HIV infection, or a variety of other illnesses probably do not need iron. I think it was Mark Goldberg's group in
Boston that showed if the serum ferritin in patients was greater than 100, you reached maximal efficacy with erythropoietin, as measured by reticulocyte rates or blood
production. Ferritin levels higher than that did not provide greater effect when giving erythropoietin.

DR CRAWFORD

There is a proviso in our new study design. Patients with ferritin levels of less than 100 at baseline go on iron from the start. However, for those who do not achieve
improvements in their hemoglobin or for the groups that fail, the question of mobilizing enough iron arises. Hopefully, you will not shift so much iron into the red cell
mass that they become functionally iron deficient.

DR SPIVAK

You will mobilize iron. This has been shown in patients with rheumatoid arthritis who have the classical anemia of chronic disease with a low serum iron, a low iron-
binding capacity, a low percentage of saturation, and a high serum ferritin level. They respond to erythropoietin unless other factors affect the response, such as
inflammation so intense that they cannot. However, it is not the iron. If they have adequate iron stores, they will respond.

DR LEE

I formerly used this logic to avoid iron supplementation in our chemoradiation therapy patient population. In our first four patients treated with erythropoietin but
without iron supplementation, hemoglobin levels dropped during chemoradiation therapy. We then changed the protocol to include oral ferrous sulfate for 12 patients.
All but one maintained hemoglobin at more than 10 g%, and their median hemoglobin nadir was 11.8 g%. There was a tremendous effect of iron supplementation in our
patient population. In lung cancer, we do not expect iron deficiencies, not like the gastrointestinal or gynecologic cancers.

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