Anemia in cancer and critical care patients: Pharmacoeconomic considerations

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Purpose. The elements and limitations of pharmacoeconomic models, types of analytic methods used in pharmacoeconomic evaluations, outcomes used in studies of anemia treatments, and comparative efficacy and cost-effectiveness of the two available erythropoietic therapies in the treatment of anemia in cancer and critical care patients are discussed.

Summary. Clinical, humanistic, and economic outcomes should be taken into consideration in pharmacoeconomic models. The validity of such models may be compromised by a lack of outcome data, unreasonable assumptions, the heterogeneity of the patient population, patient selection bias in comparative studies, and inconsistent use of instruments to measure outcomes. The degree of anemia in patients with cancer correlates with health-related quality of life (QOL). Erythropoietic therapy increases hemoglobin concentrations and QOL, reduces the need for blood transfusions, and is cost-effective for treating anemia in cancer and critical care patients. Epoetin alfa may provide a more rapid hemoglobin response and improvement in QOL at a lower cost than darbepoetin alfa. Front loading with weekly doses of either erythropoietic agent followed by a three-week-long dosing interval for maintenance treatment may be used to quickly correct anemia, improve convenience, and reduce costs.

Conclusion. Erythropoietic therapy for the treatment of anemia in cancer and critical care patients is cost-effective.

Index terms: Anemia; Blood; Costs; Critical illness; Darbepoetin alfa; Dosage schedules; Drug comparisons; Epoetin alfa; Hematopoietic agents; Methodology; Models; Neoplasms; Outcomes; Pharmacoeconomics; Quality of life

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The economic burden of anemia is substantial. A retrospective analysis of administrative claims data from 1999 to 2001 found that the difference in average annual direct costs between patients with and without anemia amounted to $29,511 for patients with congestive heart failure, $20,529 for patients with chronic kidney disease, and $18,418 for patients with cancer. Although anemia is a potentially costly condition, the cost of anemia treatment (particularly erythropoietic therapies and blood transfusions) also can be substantial. Adverse effects and the cost of treating these effects should be considered, particularly when the use of transfusions is contemplated. Making decisions about how to manage anemia is complicated by limitations in available financial resources. Years ago the cost of therapy was not a major concern, but it is an important consideration today.

Pharmacoeconomic studies of the use of erythropoietic therapies for the management of anemia in cancer and critical care patients have been performed. However, guidelines for making decisions about whether to use these therapies are not yet available because of the heterogeneity of patients, variability in treatment approaches and dosing strategies for erythropoietic agents, and lack of agreement among clinicians about the threshold hemoglobin concentration at which to initiate therapy. Anemia differs from some other medical conditions in that providing no treatment is an option to consider.

Pharmacoeconomic models

Pharmacoeconomic models are developed to facilitate decision making when data are limited, causing uncertainty. Models are only as good as the assumptions on which they are based on the proceedings of a symposium held June 26, 2006, during the ASHP Summer Meeting in Orlando, FL, and supported by an educational grant from Ortho Biotech. Dr. Reeder received an honorarium for his participation in the symposium and for the preparation of this article.
based; models based on unreasonable assumptions yield unreasonable results. Changing the assumptions often affects the conclusions drawn from a model.

The population of patients with anemia varies considerably because of the many possible causes of anemia, treatment approaches, and desired outcomes. Ideally, models are based on the results of large, randomized, double-blind, controlled clinical trials involving patients with similar characteristics (e.g., age, type and severity of disease) so that the response to treatment can be predicted. However, in reality, models often are based on limited data, especially when critical care patients are involved because the number of patients available for study is usually small. Selection bias in comparative studies (i.e., failure to randomly assign patients to the therapeutic interventions being compared) limits the ability to make meaningful conclusions. The efficacy rates observed in clinical trials usually are higher than the effectiveness rates measured in a real world setting because of differences in inclusion and exclusion criteria and outcome measures. The ability to generalize the results of multiple studies may be compromised by the use of different instruments to measure outcomes (e.g., health-related quality of life [QOL] scales). Nevertheless, pharmacoeconomic models of erythropoietic therapies provide valuable insights to help guide treatment decisions despite the limitations and shortcomings of these models.

The Economic, Clinical, and Humanistic Outcomes model (also known as the ECHO Model) provides a theoretical framework for measuring the value of a pharmaceutical product or service. This model goes beyond consideration of traditional clinical outcomes to include humanistic outcomes (e.g., QOL) and economic outcomes. Weighting the three types of variables is a balancing act that often involves tradeoffs among the relative importance variables. Use of the model can be helpful in making decisions about how to allocate limited financial resources.

Pharmacoeconomic evaluations use one of four methods (Table 1). In a cost–benefit analysis, outcomes are measured monetarily, and it is possible to determine a financial return on investment. By contrast, outcomes are measured in natural units (e.g., transfusions avoided, increase in hemoglobin concentration) when a cost–effectiveness analysis is performed. Cost-effectiveness analyses are preferred over cost–benefit analyses for pharmacoeconomic evaluations of anemia treatments because it is difficult to assign a monetary value to outcomes from these treatments.

Cost-minimization analyses are used when the outcomes of two or more therapeutic interventions are therapeutically (clinically) the same (e.g., a two-year increase in survival time for both comparators); when outcomes are the same, these analyses can be used to determine which intervention is least expensive. Cost–utility analyses take into consideration patient preferences for the effects of treatment on QOL and allow comparison of the increase in quality-adjusted life years (QALY) associated with two or more therapeutic interventions.

### Anemia treatment outcomes

Outcomes and endpoints that are often used in pharmacoeconomic evaluations of anemia treatment are listed in Table 2. The choice among these outcomes and endpoints is based on what is meaningful and valued (i.e., meaningful outcomes that are valued highly receive greater emphasis than those of lower value).

Economic endpoints include direct and indirect costs while economic outcomes are reported as pharmacoeconomic ratios (e.g., cost–effectiveness ratio, cost–utility ratio). Direct costs include the costs of items used in the treatment process, such as the costs for medications, hospital care, and physician visits. The costs of absenteeism and presenteeism (i.e., diminished functional capacity of an employee while on the job) are included in indirect costs.

Various instruments may be used to measure health-related QOL, including the Functional Assessment of Cancer Therapy (FACT) general questionnaire, a longer form of FACT that is specific for anemia (commonly known as FACT-An), and the lineal analog self-assessment scale (see the article by Schwartz in this supplement). The Medical Outcomes Study Short Form 36 (commonly referred to as SF-36) has been used to measure physical and mental aspects of health-related QOL in patients with cancer-related anemia, although the SF-36 is not cancer-specific.

Clinical endpoints tend to be easier to measure than QOL and other humanistic endpoints and some...
Economic costs (e.g., indirect costs). For example, hemoglobin levels are routinely measured and documented in the patient chart; however, the cost of providing the laboratory service is not quantified so easily. Likewise, measures of quality of life are not typically administered and recorded in the patient record. However, humanistic endpoints, such as the FACT-An, are an important consideration in treatment, especially when two treatments have the same efficacy but different effects on quality of life.

The degree of anemia in patients with cancer correlates directly with health-related QOL and patients’ ability to work, socialize, and take care of themselves and their families. Patients with a hemoglobin concentration of 12 g/dL or higher have a greater health-related QOL than those with lower hemoglobin levels.

In a retrospective analysis of 8569 hospitalized patients with heart failure, high hemoglobin concentrations were associated with a shorter hospital length of stay, lower hospital charges, and longer survival compared with lower hemoglobin concentrations. For every 1-g/dL increase in hemoglobin concentration, there was a significant 5% reduction in length of stay, a 4% decrease in charges, and a 9% reduction in mortality risk. These relationships probably can be generalized to other patient populations, including critical care and cancer patients.

Erythropoietic therapies

Epoetin alfa and darbepoetin alfa both have been shown to significantly reduce transfusion requirements in separate randomized, double-blind, placebo-controlled trials of cancer patients with chemotherapy-induced anemia. Commonly used regimens of epoetin alfa (40,000–60,000 units s.c. every week) and darbepoetin alfa (200–300 µg s.c. every 2 weeks) were compared in a randomized, open-label, nonrandomized, proof-of-concept pilot study of 20 cancer patients with chemotherapy-induced anemia. Ten patients with an increase in hemoglobin concentration of at least 2 g/dL after at least 8 weeks of treatment with the initial dosage were entered into the maintenance

<table>
<thead>
<tr>
<th>Table 2. Endpoints and Outcomes Used in Pharmacoeconomic Evaluations of Anemia Treatments</th>
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<tbody>
<tr>
<td>Clinical</td>
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<tr>
<td>• Change in hemoglobin concentration</td>
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<tr>
<td>• Duration of hemoglobin response</td>
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<tr>
<td>• Overall or progression-free survival</td>
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<td>• Need for blood transfusions</td>
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<tr>
<td>• Physical and cognitive disability/ability to perform the activities of daily living</td>
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<td>• Need for hospitalization and hospital length of stay</td>
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<tr>
<td>Economic</td>
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<tr>
<td>• Direct costs</td>
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<tr>
<td>- medical costs (e.g., charges for medications, transfusions, laboratory tests, physician visits, and hospitalization)</td>
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<tr>
<td>- nonmedical costs (e.g., housekeeping expenses at home)</td>
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<tr>
<td>• Indirect costs (e.g., lost productivity)</td>
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<tr>
<td>• Pharmacoeconomic ratios</td>
</tr>
<tr>
<td>- cost-effectiveness, cost-minimization, cost–utility ratios</td>
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<td>- cost–benefit ratios</td>
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<tr>
<td>Humanistic</td>
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<tr>
<td>• Health-related quality of life</td>
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<tr>
<td>• Ability to perform the activities of daily living</td>
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<td>• Cognitive function</td>
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<tr>
<td>• Social and emotional well-being</td>
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<td>• Satisfaction with care (e.g., avoidance or minimization of adverse effects)</td>
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Front loading (i.e., the use of large initial doses) of erythropoietic agents is a new approach that has been used to increase the efficiency of anemia management by providing prompt correction of anemia and alleviation of anemia symptoms. The use of epoetin alfa 60,000 units s.c. once weekly initially followed by 120,000 units s.c. every 3 weeks for maintenance therapy was evaluated in an open-label, nonrandomized, proof-of-concept pilot study of 20 cancer patients with chemotherapy-induced anemia. Ten patients with an increase in hemoglobin concentration of at least 2 g/dL after at least 8 weeks of treatment with the initial dosage were entered into the maintenance
phase. The mean hemoglobin concentration was 10.1 g/dL at baseline, 11.1 g/dL after 4 weeks of treatment, and 13.0 g/dL after 8 weeks, reflecting a 1.0-g/dL increase from baseline over 4 weeks and a 2.9-g/dL increase over 8 weeks. The mean hemoglobin concentration increased slightly to 13.3 g/dL during the maintenance phase in these patients, demonstrating that giving epoetin alfa every 3 weeks is effective for maintaining the hemoglobin response achieved during the initiation phase.

Front loading of darbepoetin alfa was evaluated in a randomized, open-label, phase II study of 242 patients with chemotherapy-induced anemia. In the initial hemoglobin correction phase, patients received 4.5 µg/kg or a fixed dose of 325 µg (i.e., 4.6 µg/kg for a 70-kg person) of darbepoetin alfa s.c. once weekly until a hemoglobin concentration of at least 12.0 g/dL was achieved. The same dose was then given every 3 weeks during the maintenance phase until the end of the 16-week treatment period.

High hematopoietic response rates (84% in the weight-based dosing group and 86% in the fixed-dose group) were observed. The median time to hematopoietic response was 36 days in the weight-based dosing group and 34 days in the fixed-dose group. The target hemoglobin concentration was maintained throughout the maintenance phase. The percentage of patients requiring transfusions was 16% in the weight-based group and 19% in the fixed-dose group.

Front loading of epoetin alfa and darbepoetin alfa with weekly doses to quickly correct anemia, followed by doses at 3-week intervals to maintain the desired hemoglobin concentration, represents a new paradigm. The long dosing interval during maintenance treatment may improve convenience and reduce costs.

The Agency for Healthcare Research and Quality (AHRQ) reviewed the available evidence on the comparative effectiveness of epoetin alfa and darbepoetin alfa for managing anemia in patients undergoing cancer treatment. In 2006, AHRQ released a report based on the results of this review. No clinically significant difference between the two agents was found in hemoglobin response, reduction in the need for transfusions, or thromboembolic events. There was insufficient evidence to draw conclusions about the effects of either agent on QOL, tumor response or progression, or survival.

The National Institute for Health and Clinical Excellence, an independent organization that provides evidence-based guidance on appropriate treatment to the National Health Service in the United Kingdom, conducted a comprehensive analysis of the available evidence on the use of epoetin alfa in patients with chemotherapy-induced anemia. An overview released in 2006 concluded that there is consistent evidence that administration of epoetin alfa reduces the risk for transfusions and the number of units transfused in patients with cancer. There is strong evidence that epoetin alfa improves hematologic response in patients with a baseline hemoglobin concentration less than 10 g/dL. However, there is inconclusive evidence whether epoetin alfa improves tumor response and overall survival, and research on side effects is inconclusive.

The results of two randomized, double-blind, placebo-controlled studies were used to develop two decision analytic models of the cost-effectiveness of using epoetin alfa to reduce the need for transfusions in critical care patients. Significant increases in hemoglobin concentration and reductions in transfusion requirements were demonstrated with epoetin alfa in both studies. In the model based on the first study, the incremental cost per patient of using epoetin alfa to reduce the need for transfusions was $1918 and the incremental gain in effectiveness was 0.0563 QALY, which translates into a cost-effectiveness (utility) ratio of $34,088 per QALY. The investigators considered values less than $50,000 per QALY worthwhile, although many commonly used therapies have much higher thresholds (i.e., $80,000–$100,000 per QALY) than the $50,000 benchmark, which is somewhat dated and perhaps even arbitrary. In the model based on the second study, the incremental cost per patient of using epoetin alfa to reduce the need for transfusions was smaller ($1439), largely because a lower dose was used. However, the incremental effectiveness also was smaller (0.0305 QALY), yielding a cost-effectiveness ratio of $47,149 per QALY. When a restrictive strategy using a threshold hemoglobin of approximately 21% for transfusion to maintain a hematocrit above 30% was incorporated into the models instead of the target hematocrit of 38% used in the two studies, the overall cost-effectiveness ratio was $145,455 per QALY. This ratio exceeds even the higher thresholds commonly used today to benchmark acceptable cost-effectiveness ratios.

A sensitivity analysis revealed that the risk of developing a nosocomial bacterial infection attributable to transfusion was the most important factor contributing to the incremental cost-effectiveness of epoetin alfa in both models. Assuming a willingness to pay $50,000 per QALY, epoetin alfa was considered cost-effective if the risk of nosocomial infection from one transfusion was more than 36% in the first study and more than 46% in the second study.

An economic model was created by Bramley and colleagues to compare the expected cost of treatment per patient and the cost of a hematopoietic response from 18 weeks of treatment with epoetin alfa or darbepoetin alfa in patients with lung cancer and anemia. A he-
Gene therapy has been used in the treatment of various diseases. However, cost-effectiveness ratios for gene therapy are currently lower than those for vaccines. The cost-effectiveness ratio for vaccines is higher than that for gene therapy because the effectiveness of gene therapy is not as high as that of vaccines.

Vaccination is highly effective for hepatitis B, and the cost-effectiveness ratio for hepatitis B vaccination in young adults is relatively low and varies widely for different vaccines. For example, the cost-effectiveness ratio for the hepatitis B vaccine is $19,900 versus $11,667, respectively, which is based on the unpublished results of a study in patients with lung cancer.

Conclusion
Pharmacoeconomic models demonstrate that the cost-effectiveness of treating anemia in cancer and critical care patients is cost-effective. Epoetin alfa may provide a more rapid hemoglobin response and improvement in QOL at a lower cost than darbepoetin alfa. However, cost-effectiveness ratios for the use of antihypertensive therapy vary widely because of the heterogeneity of patients with various ages and underlying diseases (e.g., cardiovascular disease, diabetes mellitus, peripheral vascular disease) and the wide variation in cost of medications used to treat hypertension (e.g., inexpensive diuretics, more costly angiotensin II receptor blockers).

The cost-effectiveness of treating anemia in cancer and critical care patients also varies widely because of the heterogeneity of patients in terms of age, severity, and survival times. Variability in estimates of the cost-effectiveness of treating anemia can be reduced by limiting the scope of pharmacoeconomic studies and models to homogeneous subgroups of patients (e.g., elderly patients with certain types of malignancy and a similar extent of disease).

Pharmacoeconomic studies provide decision-makers with a sense of relative value of therapeutic alternatives. The ratios should not be the sole determinant for therapy choice. Pharmacoeconomic ratios do provide useful information about the most efficient treatment alternative (i.e., which therapy delivers the desired outcome at the lowest cost). While benchmarks like $50,000 per QALY have been suggested, these thresholds are subjective. Use of any therapy should be a function not only of efficiency, but also the expected health benefits relative to existing alternatives.

References