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Economic evaulation of new drugs

Recombinant erythropoietin and blood transfusions in cancer chemotherapy-induced anemia

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Anemia represents a common side effect of cancer chemotherapy, and results in diminished overall well-being as well as side effects such as dyspnea, fatigue and decreased appetite. Treatment options for chemotherapy-induced anemia are transfusion of red blood cells and s.c. erythropoietin. Although transfusion is generally well tolerated, patients usually experience fluctuating hemoglobin levels because of hesitancy to transfuse to normal hemoglobin levels. Additionally, concerns persist related to the safety of blood products, including the transmission of blood-borne pathogens, immunomodulation by transfusion and severe allergic reactions, despite advances in transfusion medicine. Erythropoietin is an effective alternative to transfusion in many patients and allows for a more consistent hemoglobin level. The costs associated with the drug have limited its use. In addition, patient preferences for the two treatment options have not been investigated. Economic analyses, including consideration of the costs associated with medical care as well as the consequences, will be essential in evaluating the potential of transfusions and erythropoietin in treating the anemia associated with cancer chemotherapy. [© 1998 Lippincott Williams & Wilkins.]

Key words: Anemia, blood transfusion, chemotherapy, erythropoietin.

Introduction

Cancer-related anemia

The anemia associated with cancer is most often the anemia of chronic disease, characterized by inappropriate utilization of adequate iron stores, shortened red blood cell survival times and inadequate erythropoietin production.[1-3] Myelosuppressive chemotherapy can exacerbate or cause anemia in patients with cancer. Other causes of anemia in patients with cancer include blood loss (usually from the gastrointestinal tract), bone marrow infiltration with malignant cells, hemolysis and nutritional deficiencies.[2,4]

The anemia associated with cancer heightens the fatigue, lethargy, difficulty with concentration, anorexia and diminished well-being that occur as a result of the underlying cancer and its treatments.[1,5] Fatigue is particularly debilitating in cancer patients and its importance is probably not recognized by health care providers.[5] Quality of life measurements such as the Functional Assessment of Cancer Therapy-Anemia scale (FACT-An) and linear analog scales have demonstrated declines in quality of life as the hemoglobin decreases.[6,7] Symptoms are generally insidious and non-specific, and may not be recognized as being due to the anemia as well as the cancer and the cancer treatments. In patients with compromised cardiovascular status, anemia may be particularly troublesome.

The incidence of chemotherapy-induced anemia varies according to the type of malignancy, the stage of the disease, and the type, dose and schedule of chemotherapy therapy.[1,8] As one might predict, patients who are anemic before beginning chemotherapy are more likely to be treated for anemia than those who are not.[9]

Treatment of chemotherapy-induced anemia

The decision to treat anemia related to chemotherapy depends upon the degree and expected duration of the anemia, symptoms associated with the anemia and the patient's health status, including the presence of cardiac and lung disease. The threshold for treatment also varies among providers. Most patients are treated once the hemoglobin approaches 8.0 mg/dl.[10] In a

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study of over 350 cancer patients undergoing chemotherapy, 18% of those with solid tumors were transfused with red blood cells. This increased to 34% among the 53 patients with lung cancer; lung cancer patients were also transfused at a higher hemoglobin value than the other patients, most likely due to the presence of pre-existing lung disease.[9]

Treatment options for chemotherapy-induced anemia include transfusion of red blood cells and, more recently, s.c. or i.v. recombinant human erythropoietin (rhEpo). Other treatable causes of anemia, mentioned above, should be ruled out before initiating therapy.

Transfusion of red blood cells is the most rapid and reliable way of increasing the hemoglobin level. In the absence of bleeding or hemolysis, an adult patient's hematocrit will increase predictably by approximately 3–4% per unit of packed red blood cells. Current screening methods for blood-borne viruses have dramatically reduced the risk of transfusion-acquired infection such as the human immunodeficiency virus to 1:493 000 units (0.0002%), and HTLV-I and HTLV-II to 1:641 000 units (0.0016%). Since the advent of testing for hepatitis C, the risk of transfusion-acquired hepatitis C infection has fallen to 0.00097% per unit.[11] Nonetheless, up to 20% of patients may experience adverse effects such as fever, chills, urticaria, circulatory overload and severe allergic reactions.[12] Other considerations are the possibility of transfusion-induced immunomodulatory effects that may increase the risk of recurrence or progression of cancer,[13,14] the risk of iron overload in patients receiving multiple transfusions and, rarely, the risk of graft-versus-host disease (GVHD). Some risks, including post-transfusion fever, chills, transmission of cytomegalovirus, alloimmunization to histocompatibility antigens and immunomodulation can be substantially (>90%) reduced by use of leukocyte-depletion filters. Most of the data supporting the use of leukocyte depletion has been in surgical patients or those with acute leukemia. These issues have not been adequately studied in patients with solid tumors. While almost all patients with hematologic malignancies in the US now receive leukocyte-depleted blood, the patterns of practice in other oncology patients vary enormously. Although the risk of life-threatening GVHD is very low, irradiation of cellular components (e.g. red cells or platelets) to 25–30 cG probably abrogates this risk completely. Irradiation of red cell or platelet transfusions should be considered for patients undergoing high-dose therapy or who are known to be anergic or otherwise immunosuppressed.

Because of the above-mentioned risks and despite the low risk of transfusion-acquired infection, patients and their physicians may be reluctant to transfuse often enough to maintain a near-normal hemoglobin. Indeed, it is currently considered questionable practice to transfuse to near-normal hemoglobin despite potential improvements in quality of life. Receiving transfusions is inconvenient for the patient, requiring phlebotomy, and waiting for matching of the blood product, venous access and several hours for the procedure. It is our experience that most patients with chronic anemia are transfused only when their hemoglobin falls below 10 mg/dl or even lower. Many of our patients refuse transfusion until they are experiencing severe symptoms of anemia. Even in patients who are regularly transfused, hemoglobin values fall between transfusions and patients may be anemic for a significant proportion of the time.

Recombinant human erythropoietin, first approved for the treatment of anemia associated with end-stage renal disease (ESRD), provides another option in patients with anemia related to cancer and its treatment. Erythropoietin is most commonly given s.c. three times a week starting with a dose of 100–150 IU/kg. In patients who do not respond to this dose after a 2–4 week period or in those with thrombocytopenia, up to 300 IU/kg thrice weekly may be required. Increases in the dose beyond this are not recommended given the low likelihood of response.[15] Interestingly, a recent study of patients with small cell lung cancer found that some patients responded to doses of only 25–30 IU/kg, a dose clearly much lower than that commonly used.[16]

Erythropoietin has also been used to prevent the anemia that occurs with intensive chemotherapy. In a randomized study of 62 patients receiving dose-intense chemotherapy for early-stage breast cancer, the hemoglobin levels in the patients receiving erythropoietin did not change, while those on the no erythropoietin arm had a mean hemoglobin decrease of approximately 3 g/dl.[17]

Serious adverse events from erythropoietin are rare. Among patients with chronic renal failure, hypertension, seizures and venous thromboses may occur in patients whose hematocrit rises above 38% or in those with underlying hypertension.[18,19] Such side effects appear to be rare, although not unheard of, among non-dialysis patients.

The disadvantages of erythropoietin are its cost and the fact that, at least in the US, many insurance companies cover the cost of the drug if it is given in a physician's office but do not cover the drug if it is given at home. This requires that patients travel to the site of administration, increasing the patients' time and travel costs. Additionally, not all patients will respond to erythropoietin and some of those who do respond will require ongoing transfusions during the initial trial

of the drug or thereafter. Responses, usually defined as an increase in hemoglobin of 2 g/dl (or a 6% increase in hematocrit), have occurred in 30–80% of cancer patients treated with erythropoietin with most studies demonstrating a 50% response rate.[18,20–24] Patients may occasionally become transfusion independent.[7,22] The variation in response rates is most likely the result of differences in patient populations (cancer diagnosis and severity of disease), dose of the drug, duration of therapy, status of iron stores and definitions of response. Advanced age and the presence of neoplastic bone marrow infiltration do not influence the likelihood of response to the drug.[25,26]

One way to reduce the cost of erythropoietin is to select patients who are most likely to respond to the drug, thereby avoiding a 1–2 month trial of the drug in those destined to be non-responders. For example, it is recommended by some that pretreatment endogenous serum erythropoietin levels may predict response to exogenously administered erythropoietin.[15] If the erythropoietin level is lower than that predicted for the degree of anemia, the patient is more likely to respond to administration of the drug. If, on the other hand, the serum erythropoietin level is in the range consistent with adequate erythropoietin production, administering erythropoietin, even in high doses is not likely to lead to a response. A graphic representation of the relationship of hematocrit to serum erythropoietin was recently published.[15] Although such an approach is appealing, other investigators have demonstrated little correlation between the pretreatment serum erythropoietin level and the degree of response.[18,27,28] This was particularly the case in patients receiving chemotherapy.[22]

One study of cancer patients using stepwise discriminant analysis generated a predictive algorithm for non-response after a brief trial of erythropoietin. Erythropoietin and hemoglobin were measured after 2 weeks of treatment with thrice-weekly erythropoietin. If after 2 weeks the serum erythropoietin level was less than 100 mU/ml and the hemoglobin concentration had increased by 0.5 mg/dl or more, the patient was most likely going to be a responder (predictive power of 95%). If, on the other hand, the serum erythropoietin level was greater than or equal to 100 mU/ml and the increase in hemoglobin was less than 0.5 g/dl, the patient was most likely not going to respond to ongoing treatment (predictive power of 93%). The authors also found that 75% of patients with a serum ferritin level less than 400 ng/ml after 2 weeks would respond to erythropoietin while those with a level greater than 400 ng/ml were likely to be non-responders (predictive power of 88%). A validation set of subjects confirmed the model.

Economic analysis in the treatment of cancer-related anemia

The assumption underlying the use economic analyses of health-care interventions is that health-care resources are limited and should be directed toward health strategies that provide the most benefit per dollar spent. Even in the absence of an explicit budgetary constraint, there is an implicit need to control spending. Consensus-based guidelines for the conduct of these analyses have been developed by the Panel on Cost-Effectiveness in Health and Medicine, convened by the US Public Health Service in 1993. The Panel advised, among other things, that a societal perspective, rather than the perspective of individuals, third-party payers or health-care providers, be taken for both costs and benefits.[29,30]

Cost–effectiveness analysis (CEA)

CEA is a tool used to compare the resource use (costs) and health outcomes (effectiveness) associated with two or more management or diagnostic strategies. One treatment option, e.g. a new drug, is compared to the standard treatment (or treatments) to determine the incremental costs (either greater or lesser) and incremental effects (again, either greater or lesser) of the new treatment. Costs make up the numerator and effects the denominator of the cost-effectiveness ratio. In a CEA, the effects are expressed as 'natural units,' such as years of life saved, surgeries avoided or improvements in quality of life, so that the ratio expressed as cost (in $) per year of life saved, etc. In a CEA of erythropoietin or transfusion for chemotherapy-related anemia, the natural unit might be 'cost per transfusion avoided' or 'cost per one-point increase in quality of life'.

Cost–utility analysis (CUA)

CUA is a type of CEA, but differs from CEA in that the denominator is quality-adjusted life-years (QALYs). QALYs are determined by multiplying the number of years of life by a quality adjuster (also called utility). This quality adjuster is a number from 0 ('dead') to 1 (often 'perfect health') that is used in an attempt to generate a composite measure of quality of life and life expectancy. Measuring utility attempts to capture the values, or preferences, that patients have for different health states. The use of utility may be particularly appropriate when the intervention being studied is a

supportive measure rather than a life-saving measure. In a cost-utility model, the results are expressed as 'cost per QALY'.

Many methods have been used in the measurement of utility [rating scale, time trade-off (TTO) and standard reference gamble].[31-33] For the rating scale method of assessing utility, respondents are shown a line with clearly-defined ends (often death at the left-hand end and perfect health at the right-hand end). Participants are asked to choose a point along the line to indicate where they would place a particular health state. In the TTO method, participants are asked how much time they would be willing to trade-off to achieve better health. The time the respondent is willing to give up is varied until a point of indifference is reached. In the standard reference gamble method, participants are asked to choose between a certain particular health state and a gamble associated with a probability of returning to normal health (p) and a probability of certain death ($1-p$). The probability of returning to normal health is varied until the respondent is indifferent between the chronic health state and the gamble. For all three methods, respondents may be asked to consider their own current health state or a hypothetical health state. Little agreement exists as to which method for elicitation of utility is the 'gold standard'. Several authors have demonstrated that the results of health-state questionnaires and utility measures are not interchangeable,[31,34] and that the utility values obtained with one method are not interchangeable with those of another.[33,35,36]

Another area of debate is the question of whose utilities should be measured—those of society in general or those of the people who have experience with the condition or treatment under investigation.[37-39] The preference for a particular health state is generally higher when the participants have experienced the health state[37] or when the use of an intervention is likely to benefit themselves.[38] From the point of view of a health policy maker in the position of deciding how to allocate limited resources, however, societal values must be measured and considered. As described above, the Panel on Cost-Effectiveness in Health and Medicine recommend that a societal perspective be taken for CEA and CUA.[30]

Cost–benefit analysis (CBA)

CBA attempts to measure both costs and consequences in monetary terms. If the benefits are savings in medical care costs, this method is fairly straightforward. The 'human capital approach' was originally used as a means of valuing benefits. Improved health would increase productivity and wages could be used to assess improvements in outcome. This major limitation of this method is that it is biased against retired workers, children, volunteers and women who do not work outside the home. In addition, assigning improvements in quality of life a monetary value is also problematic and makes CBA less palatable to the medical community. Assessment of societal willingness-to-pay for an intervention is another way of assigning a monetary value to an intervention.[40] Respondents are asked how much money they would be willing to contribute to have the intervention under consideration, whether that be a treatment, a diagnostic test or a procedure. As with measurement of utility, the perspective of members of the society at large would be more consistent with a society perspective than that of respondents experienced with the disease state and its treatment.

Incremental cost–consequence analysis

When two competing treatment strategies are being considered, such as erythropoietin and transfusions in the treatment of chemotherapy-induced anemia, the *incremental* costs and benefits are of primary importance. The incremental ratio, i.e. the difference in costs between the two strategies divided by the difference in benefits, must be calculated. This approach may lead to selection of a less expensive, although somewhat less beneficial, treatment strategy. Of course, in the case of treatment for anemia, the two treatment options are not mutually exclusive. A patient on erythropoietin may continue to require transfusions, although one would hope less often. Additionally, differences in individual patients or in types of patients will lead to differences in the cost-effectiveness ratio. For example, in a patient who requires frequent transfusions, continuous erythropoietin will be a more cost-effective treatment strategy than in a patient who requires transfusion only rarely.

Measuring the consequences of treatment with transfusions and erythropoietin

The consequences of transfusions and erythropoietin may be measured in terms of increase in hemoglobin, e.g. the ability of the 1 unit of blood or 1 month's of erythropoietin to increase the hemoglobin by 1 g. Another approach would assess the improvements in

quality of life with the two treatments or, alternatively, the utility associated with the two treatments. In this case, the *incremental* benefits of erythropoietin compared with transfusion are difficult to separate from the benefits of treating the anemia. Patients with both ESRD and cancer who have an increase in hemoglobin while on erythropoietin experience a concomitant improvement in functional status and quality of life (as assessed by a variety of instruments).[4,7,21,41] These patients may have experienced the same improvements in these parameters if they were transfused to maintain the higher hemoglobin values they achieved on erythropoietin. It is possible that a more constant hematocrit while on erythropoietin allows patients to experience greater quality of life than they would have with the fluctuating levels achieved with transfusions. Interestingly, among patients with ESRD the Canadian Erythropoietin Study Group found no differences in psychosocial aspects of health or in utility as measured by the TTO method.[42] That is, despite improvements in exercise tolerance, the utility in the patients was no different in the transfusion-treated group compared with the erythropoietin-treated group in this placebo-controlled, randomized trial. There are no published studies assessing utility or willingness-to-pay in associated with erythropoietin and transfusions, so CUA and CBA of these two treatment options cannot as yet be performed.

One challenge in comparing the consequences of treatment with erythropoietin as opposed to the conventional approach of transfusions is the poorly characterized safety of transfusion in ambulatory oncology practice. While transfusion in surgical oncology settings has been associated with the dramatically increased incidence of post-operative infections likely preventable by leukocyte depletion of red blood cells, it is not known whether transfusions for chronic anemia would have a similar effect. In addition, transfusions in the surgical setting may be associated with more frequent or earlier tumor recurrences although this is less clear than the associated with postoperative infections.[14] It is unknown whether transfusions for chronic anemia might be associated with lower success rates for curative chemotherapy or accelerated tumor growth in patients undergoing palliative treatment. These issues of transfusion safety potentially outweigh by an order of magnitude or more the well-characterized and accepted risks of transfusion. Given the centrality of these issues to the clinical outcomes and economic analyses most of interest in patients with cancer, a meaningful comparison of the efficacy, safety and cost-effectiveness of transfusions versus erythropoietin awaits investigation of these issues.

Costs of treatment with transfusions and erythropoietin

The costs to consider with both treatment strategies are listed in Table 1, and include both direct (medical and non-medical) costs and indirect costs. (Whenever possible, the costs associated with the production of the medical care, rather than the charges, should be used when comparing two or more treatment options.[29] Charges, although of interest to individuals or to third-party payers, may misrepresent the actual costs associated with production of care.) In a cost-utility model, indirect costs such as lost productivity and the intangible treatment effects may be incorporated into the measure of QALYs, and in that case must not be 'double-counted' in both the numerator and the denominator.

Costs associated with blood transfusions are clearly more than just the blood product itself. One study of 19 US teaching hospitals concluded that the average price per unit of blood, including the acquisition, blood bank handling, laboratory testing and administration costs, was $155.[43] This study did not include a consideration of transfusion aberrancy or adverse event evaluations. Similarly, a multicenter study conducted in Canada concluded that the mean cost of each unit of blood is Canadian $210. The estimate most commonly used in discussions of the costs of transfusion is between $150 and 460 per unit or $300–900 per two-unit transfusion.[44–46] One study concluded, however, that the cost per episode (up to two units per episode) would approach $1700, including costs of evaluation of aberrancies in the blood bank, and at the bedside, venipuncture, premedication and white cell reduction filters.[8] Although the cost estimate in this latter study is far and above the usual estimate, this is the most inclusive approach from a societal point of view. Given that the risk of transfusion-acquired infection is exceedingly low, incorporating the costs of treating such infections is difficult. Although non-zero, these costs are probably negligible in a cost-consequence analysis. The indirect costs listed in Table 1 are not considered in any of the above cost estimates but could be incorporated into the utility associated with the treatment. The potential costs related to transfusion immunomodulation in the out-patient oncology setting are unknown but could be considerable.

The costs of treatment with erythropoietin are simpler to estimate and include the cost of the drug, the cost of the injection procedure and the cost of treating adverse events from the drug. A 62 kg (136 lb) woman treated with 150 units/kg of erythropoietin three times a week will require approximately

Table 1. Costs associated with transfusions and erythropoietin in the treatment of chemotherapy-induced anemia

	Transfusions	Erythropoietin
Direct costs		
medical	procurement of donor blood	medication
	acquisition cost for blood product	cost of the drug
	processing of blood	dose required for response
	collection site	likelihood of response
	administration site	drug administration
	laboratory testing	costs of administration
	blood product	pharmacy
	patient	laboratory testing
	special procedures and supplies	iron supplementation
	blood irradiation	treatment of adverse effects
	leukocyte depletion filter	transfusion in event of incomplete response
	administration of blood	
	nursing	
	physician	
	cost of premedication(s)	
	evaluation of aberrancies	
	health care personnel	
	laboratory testing	
	treatment of adverse effects	
non-medical	care provided by family and friends	
	transportation to and from medical services	
Indirect costs		
wages/time	lost productivity and absenteeism	
	income lost by family members	
	leisure time foregone	
	time spent seeking medical care	
	blood donor time and travel costs	
intangible	psychosocial costs, e.g. apprehension, loss of well-being	
	physical discomfort associated with procedures (not requiring treatment)	

Table 2. Factors included in consideration of costs and effectiveness of treating chemotherapy-induced anemia with transfusions or erythropoietin

Patient and cancer	underlying malignancy
	chemotherapy (type, schedule, dose)
	target hematocrit
	presence of other medical conditions (e.g. cardiac and pulmonary disease)
	ease of access to medical services (distance, ability to drive)
	preferences regarding treatment
	timeframe (short-term versus long-term)
Transfusion	frequency of transfusion
	no. of red blood cell units required to maintain target hematocrit
	presence/absence of unusual blood type
	ability to tolerate transfusions without adverse effects (e.g. volume overload, allergic reactions)
Erythropoietin	probability of response
	dose of erythropoietin required for adequate response
	underlying iron stores

113 400 units of erythropoietin a month. At a wholesale drug cost of $90 for 10 000 units, the monthly pharmacy cost will be $1000. Multidose vials have allowed for little waste of the product. The cost of administration will be related to whether the injections are given at a medical site or at home and by a nurse or by the patient or family. If the drug is given in a out-patient medical setting, patient time and travel

costs should be incorporated into the analysis (either in the numerator or the denominator), and, if given at home, the costs of patient or family education must be included. Although adverse events from erythropoietin are unusual, the cost of treating such events should also be included in the consideration.

Summary

Largely because of the uncertainties described in the preceding sections, it is not possible at present to compare directly the safety or cost-consequence of transfusion therapy and erythropoietin in treating chemotherapy-induced anemia. Both treatments are effective in improving hemoglobin levels, but the use of transfusion to restore baseline function status and quality of life is currently not practiced because of perceived risks and costs and real inconvenience to patients. Use of erythropoietin in achieving the same goals is only beginning to be evaluated. With further data on transfusion side effects, increasing experience with erythropoietin, study of patient preferences, and a thoughtful and comprehensive approach to cost collection, some of these issues will soon be resolved.

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