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CLINICAL INVESTIGATION **Cervix**

COST ANALYSIS OF ERYTHROPOIETIN VERSUS BLOOD TRANSFUSIONS FOR CERVICAL CANCER PATIENTS RECEIVING CHEMORADIOTHERAPY

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Purpose: Red blood cell (RBC) transfusions or erythropoietin (EPO) can be used to evade the detrimental effects of anemia during radiotherapy, but the economic consequences of selecting either intervention are not well defined. The RBC transfusion needs during chemoradiotherapy for cervix cancer were quantified to allow comparison of RBC transfusion costs with the projected cost of EPO in this setting.

Methods and Materials: For patients receiving pelvic radiotherapy, weekly cisplatin, and brachytherapy, the RBC units transfused during treatment were tallied. RBC transfusion costs per unit included the blood itself, laboratory fees, and expected value (risk multiplied by cost) of transfusion-related viral illness. EPO costs included the drug itself and supplemental RBC transfusions when hemoglobin was not adequately maintained. An EPO dosage based on reported usage in cervix cancer patients was applied.

Results: Transfusions were given for hemoglobin <10 g/dL. Among 12 consecutive patients, 10 needed at least 1 U of RBC before or during treatment, most commonly after the fifth week. A total of 37 U was given during treatment, for an average of 3.1 U/patient. The sum total of the projected average transfusion-related costs was $990, compared with the total projected EPO-related costs of $3869.

Conclusions: Because no proven clinical advantage has been documented for EPO compared with RBC transfusions to maintain hemoglobin during cervix cancer treatment, for most patients, transfusions are an appropriate and appealingly less expensive option. **© 2001 Elsevier Science Inc.**

Transfusion, Radiotherapy, Erythropoietin, Cost, Cervical cancer.

INTRODUCTION

For patients with cancer of the cervix, anemia has been correlated with reduced local control rates and lower survival after radiotherapy (RT). In the 1960s, a prospective randomized study to evaluate the effect of modulating hemoglobin (Hb) levels on cervical cancer treatment outcome was conducted at the Princess Margaret Hospital. The results strongly suggested that red blood cell (RBC) transfusions improve the prognosis for anemic patients in this setting (1). Consequently, the use of RBC transfusions to correct anemia before treatment with RT entered routine clinical practice, although the true impact of transfusions on radioresistant regions of intratumoral hypoxia and local control remains a topic of continuing debate (2).

In the past several years, combined chemoradiotherapy (chemo-RT) has emerged as the standard of care for the treatment of patients with locally advanced cervical cancer (3, 4). Although some data suggest that cisplatin, in particular, might be an effective radiosensitizer for hypoxic cells (5), nevertheless, it is plausible that severe anemia might be as detrimental during combined modality therapy as it is during RT alone. For this reason, it remains common practice to maintain stable Hb levels during treatment. Given the anticipated additional treatment-related stress on the bone marrow during chemo-RT compared with RT alone, RBC transfusions might be needed more during chemo-RT than during RT alone. To assess the extent of the problem, the first objective of the present study was to quantify the RBC transfusion needs during chemo-RT for cervical cancer at a single institution where a consistent policy for transfusions during chemo-RT was applied.

Numerous reports have documented that recombinant human erythropoietin (EPO) is an effective alternative to RBC transfusions to sustain or raise Hb levels during RT (6–9). Currently, no proof is available that its use is superior to RBC transfusions with respect to the impact on clinical

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Table 1. Patient population characteristics ($n = 12$)

Median age (yr)	42 (23–81)
FIGO stage	
IB-IIB	6
III-IVA	4
Recurrence after RH	2
Median baseline hemoglobin (g/dL)	10.9 (6.5–13.4)
Cisplatin (40 mg/m^2) Cycles (n)	
6	8
4–5	4
Median whole pelvis EBRT dose (Gy)	39.6 (36–45)
Median pelvic sidewall EBRT boost dose (Gy)	10 (0–15)
Median total pelvic EBRT dose (Gy)	50.4 (45–54.6)

Abbreviations: RH = radical hysterectomy; EBRT = external beam radiotherapy.

Numbers in parentheses are the range.

outcome, and the selection of RBC transfusions or EPO for anemic patients receiving RT is a matter of physician preference. In the current health care economic climate of pressure to minimize costs whenever possible, it is appropriate to evaluate the economic implications of either strategy for correcting anemia. Therefore, the ultimate goal of the present study was to compare the costs of transfusions for cervical cancer patients receiving chemo-RT with the projected cost of EPO.

METHODS AND MATERIALS

Patient population

Although other chemotherapy regimens had been used intermittently previously, in 1999 it was agreed among physicians involved in the care of cervical cancer patients at the Medical College of Virginia (MCV) Hospitals that weekly cisplatin would thereafter be the standard regimen administered concomitantly with RT for all medically suitable patients treated with curative intent. The present study cohort was 12 consecutive, unselected patients treated in this manner with an identical dose of weekly cisplatin concurrent with pelvic RT, starting in October 1999 and continuing through the next 5 months. No patients treated during this period were excluded. The clinical characteristics of these patients are listed in Table 1. The patient cohort included 10 patients treated for de novo cancer, FIGO Stages IB-IVA, and 2 patients who had an isolated pelvic recurrence after previous radical hysterectomy. Neither of the latter 2 patients had received prior pelvic RT.

All patients received whole pelvic RT at a dose of 1.8 Gy/fraction during the 4.5–5 weeks before 2 low-dose-rate brachytherapy implants. A 4-field setup was used, with a superior border at the L4-L5 interspace. Concurrent chemotherapy consisted of weekly cisplatin, 40 mg/m^2 or a maximal weekly dose of 70 mg. Serum electrolytes, serum creatinine, and a complete blood count, including Hb level, were obtained before each weekly dose of cisplatin. Patients received the cisplatin unless the granulocyte count was below 1.5×10^6/mL. No patient received granulocyte colony-stimulating factor or EPO. In most cases, an external beam boost to the lateral pelvic nodal regions was administered between the first and second brachytherapy application to provide a cumulative external beam dose in the range of 50–55 Gy to that site.

Transfusion need determination

The patient records were retrospectively reviewed to record the pretreatment Hb, weekly Hb, and number of RBC units transfused before and during chemo-RT. The institutional policy at the MCV Hospitals is to administer RBC transfusions before and during chemo-RT if the Hb is <10 g/dL. A sufficient number of RBC units are transfused until the posttransfusion Hb rises to >10 g/dL. Patients in the present study were treated exclusively with transfusion; none received EPO at any time. It would remain our policy to administer transfusions before treatment in anemic patients for immediate correction of anemia, regardless of whether transfusions or EPO were used later to maintain the Hb above the minimal acceptable level. Thus, although the pretreatment transfusions were tallied, the primary endpoint of interest was the number of RBC transfusions administered during chemo-RT.

RBC transfusion- and EPO-related cost comparison

All direct RBC transfusion- and EPO-related costs of potential value greater than $50 were included in the cost comparison. The cost of the i.v. line supplies for RBC transfusion and syringes for EPO administration was therefore excluded. Also excluded were the person-hours of nursing labor associated with either transfusion or EPO injection, because a separate charge code is not routinely used for this service at our institution.

The total cost of RBC transfusion was calculated as the sum of charges for the blood and associated charges for ancillary laboratory testing necessary for transfusion, namely blood typing and crossmatching. When more than 1 U is transfused in the same day, the charges for typing and crossmatching subsequent units are lower. Added to the charge for the blood was an estimate of the expected value for managing any of the three major infectious illnesses known to be transmitted at a low frequency with blood transfusions (i.e., infection with human immunodeficiency virus [HIV], hepatitis B virus [HBV], or hepatitis C virus [HCV]). The expected value of cost for each infection was calculated as the risk of transmission multiplied by the average cost of managing the illness according to the most recent published cost analyses available in a peer-reviewed journal. Bacterial infection can also occur with blood product transfusions. A cost estimate for this type of complication was not included because of its extreme rarity with RBC transfusions. The economic impact of transfusion-related infectious illness with regard to lost wages and other indirect personal costs was likewise not included in the present analysis, because this information is not specifically itemized in published cost analyses pertaining to the illnesses of interest here.

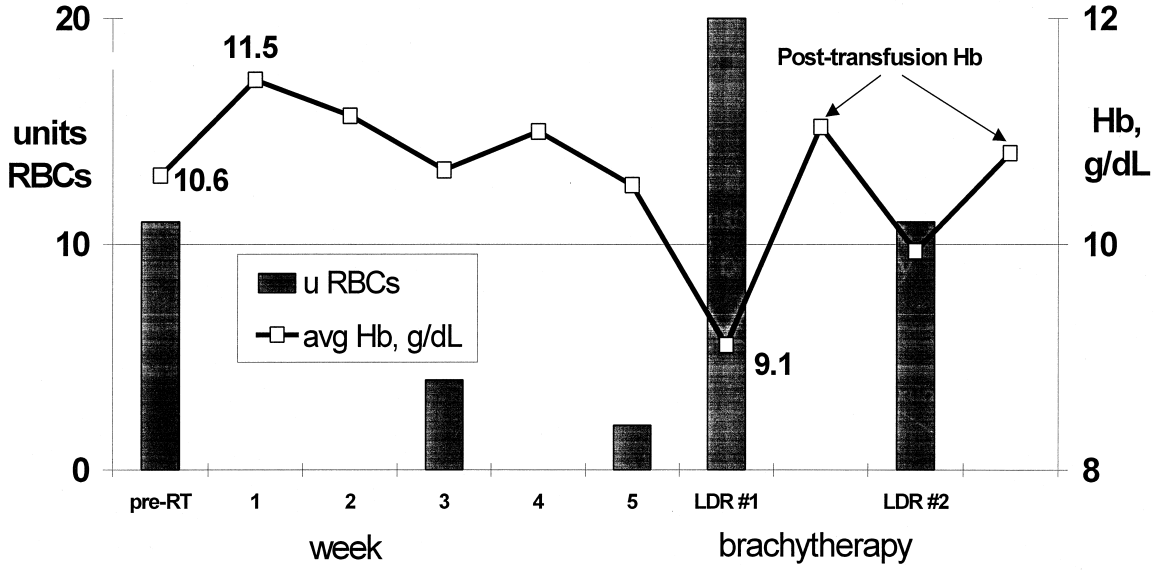

Fig. 1. Weekly Hb and RBCs units transfused. The left-sided *y* axis corresponds to the number of RBCs units (shaded bars) transfused at the time (week of external beam RT or brachytherapy implant) indicated along the *x* axis. The right-sided *y* axis corresponds to the Hb (solid black line) at the time indicated along the *x* axis. Mean baseline values at the time of diagnosis and after pre-RT transfusions are indicated near the corresponding points on the graph, as is the mean nadir value at the time of first brachytherapy implant hospitalization. Mean Hb values after any transfusions during the brachytherapy hospitalizations are also noted. LDR#1, LDR#2 = first and second low-dose-rate brachytherapy applications, respectively.

Patients occasionally experience mild, nonspecific febrile reactions to RBC transfusions. Conservative management with antipyretics and/or antihistamines is generally effective, and the cost associated with these reactions was not included. More serious anaphylactic reactions are very rare, estimated to occur in 1 in 20,000 to 47,000 transfusions (10). The associated costs were not included in the analysis, because no reports have isolated costs specific to the management of this uncommon type of reaction.

To assess the total average EPO-related cost, the cost of supplemental RBC transfusions in the event that the EPO effect was not sufficient to maintain the minimal acceptable Hb level was added to the cost of the drug itself. Also added was the expected value of the cost of managing the expected low rate of deep vein thrombosis (DVT) associated with EPO administration (6, 9), calculated in a manner similar to the cost of infections from blood transfusions as the risk of DVT multiplied by the average cost of managing DVT.

The dose schedule of EPO used to compute the EPO costs during chemo-RT was 50,000 U/wk, which represents the dose used by Throuvalas *et al.* (9) in a randomized study evaluating the efficacy of EPO to reduce transfusion needs during chemo-RT for patients with cervix and bladder cancer. This particular reference study is not only the most recently reported but also incorporated a schedule of chemo-RT nearly identical to what was used for patients in the present study (i.e., pelvic RT at 2 Gy/fraction and weekly carboplatin 90 mg/m^2).

Once the difference in cost between RBC transfusion and EPO was estimated for the baseline conditions already given, a one-way sensitivity analysis was performed to determine the impact of altering any of the key determinants of the net differential cost (11). Specifically examined were the effects of reducing the item cost of EPO, raising the cost of RBC units, or increasing the risk of infectious complications.

RESULTS

Hb levels and transfusion use

All patients received at least 5 cycles of cisplatin, and 8 received a sixth cycle either at the time of hospitalization for the first brachytherapy implant or as an outpatient during pelvic sidewall boost treatments between the 2 brachytherapy implants. Two patients required postponement of a planned cisplatin administration because of a low granulocyte count. Of the 12 patients, 4 required pretreatment transfusions to boost the Hb level >10 g/dL and 10 required at least 1 U of RBC transfusion at some point before or during chemo-RT.

The time–course relationship between Hb and RBC transfusions is illustrated in Fig. 1. A total of 37 U of RBCs was given to the 12 patients during chemo-RT (average 3.1 U/patient). As seen in Fig. 1, most transfusions given during chemo-RT were provided at the time when patients returned for hospitalization during low-dose-rate brachytherapy applications.

Cost analysis

The blood costs were determined using the current charges at the MCV Hospitals. The following charges per

unit of RBCs transfused were included: $108 for ABO typing, Rh typing, and antibody screening; $112 for cross-matching with the RBC unit to be transfused; $70 for the unit of RBCs itself; and $26 for administrative processing. The sum total of these charges was thus $316/U of RBCs. For subsequent transfused units, only the $70 blood unit charge and $26 administrative fee were applied if the transfusions were given on the same day. For the present analysis, the worst case scenario was assumed, wherein an average of 3.1 U was transfused at the full price of $316/U, matched by a new sample each time. The total cost for the RBC units alone would then average $980.

The cost of infectious sequelae was estimated for HIV, HBV, and HCV on the basis of the reported incidences and costs of managing each of these infections. The probability of contracting HIV from a blood transfusion has been estimated to range from 1 in 450,000 to 1 in 660,000/U transfused (12). Recent estimates of the average monthly costs for acquired immunodeficiency syndrome management range from approximately $1300 to $2600, depending on the disease severity (13). For a worst case scenario involving the highest monthly costs of therapy maintained during a 10-year period, roughly four times the median survival of patients with acquired immunodeficiency syndrome (14), the total cost of an HIV illness is estimated to be $312,000. The present value of these costs, determined using a projected 3% simple annual interest rate during the 10-year period and rounded to the nearest thousand, is approximately $232,000. Multiplying this amount by the high-end estimate of HIV infection by blood transfusion and the average number of transfusions given during chemo-RT, the average subtotal incremental charge from transfusion-related HIV infection in the present study population would be rounded off to $2.

The upper limit of probability of contracting HBV from a blood transfusion has been estimated to be 1 in 31,000/U transfused (15), and the direct medical costs for acute or chronic HBV infection in a developed country have been estimated to range up to $4469 and $3102 per year, respectively (16; convert 1 Deutsche Mark = $0.45). For the worst case scenario wherein all infections convert from acute to chronic and require 30 years of therapy after initial treatment, a total cost of $93,060 is estimated for maintenance treatment. The present value of this portion of the costs, again determined using a projected 3% simple annual interest rate during the 30-year period, is $38,339. Added to the $4469 estimated for management of the acute phase, a total cost of $42,808 is estimated. Multiplying this amount by the risk of HBV infection by blood transfusion and the average number of transfusions given during chemo-RT, the average subtotal incremental charge from transfusion-related HBV infection in the present study population would be rounded off to $4.

The upper limit of probability of contracting HCV from a blood transfusion has been estimated to be 1 in 28,000 (15). The total projected costs associated with an aggressive treatment strategy involving interferon and ribavirin therapy for HCV have been estimated to be $37,263 (17), largely incurred during the first year of treatment and thus considered representative of the present value of the costs. Multiplying this amount by the risk of HCV infection by blood transfusion and the average number of transfusions given during chemo-RT, the average subtotal incremental charge from transfusion-related HCV infection in the present study population would be $4.

The sum total of the projected average transfusion-related costs, including the costs associated with the management of the major viral illnesses that can be transmitted by transfusion, was thus $990.

The EPO costs were determined using the current wholesale charges to the pharmacy at MCV Hospitals. A single 10,000 U vial currently costs $125. The EPO dose and schedule applied were based on a reference study of EPO usage in a similar patient population (9). For a 6-week course of EPO at a dose of 50,000 U/wk, the cost for the EPO alone would be $3750. In the reference study, 2 of 28 patients required transfusions of 2 U of RBCs each, despite EPO use. If this risk were multiplied by the cost of the RBCs transfused, an incremental cost of just >$41 would be incurred. The incidence of DVT in patients who received EPO during RT for pelvic cancer has been cited in the range of 1 in 28 to 4 in 15 (6, 9). Although other risk factors for DVT are present in this setting, a contributory effect from EPO cannot be ruled out; a more thorough discussion of this topic is presented in the package insert accompanying commercial formulations of the product. An average cost for outpatient DVT management was recently estimated to be approximately $2194 (18). Applying the lower reported rate of DVT in this setting, 1 in 28, yields an estimated additional incremental cost of $78. The total projected EPO-related costs would thus amount to an average of $3869.

Table 2. Total cost and net cost differences between EPO and transfusion during chemo-RT for cervix cancer, varied cost input parameters

Parameter altered	EPO cost	Transfusion cost	Net difference
None (baseline)	$3869	$ 990	$2879
100-fold increase in the cost of HIV, HCV, and HBV	$3869	$1980*	$1929*
Reduce EPO cost 50%	$1994*	$ 990	$1004*
Reduce EPO cost 80%	$ 869*	$ 990	($ 121)*
Double cost per RBC unit	$3869	$1970*	$1899*
Triple cost per RBC unit	$3869	$2950*	$ 919*
Quadruple cost per RBC unit	$3869	$3930*	($ 39)*

* Variation from baseline values. Numbers in parentheses indicate instances of lower cost with EPO usage.

Sensitivity analysis

Table 2 includes the quantitative results obtained from a first-order sensitivity analysis in which the parameters contributing to the total cost estimation of transfusion or EPO were altered. The calculations were performed to determine

Table 3. Studies analyzing efficacy of EPO in raising Hb during RT

Study	Cancer type	Patients receiving EPO (*n*)	EPO dose	Mean change in Hb (g/dL)
Vijayakumar *et al.*, 1993 (8)	Lung, breast, cervix, prostate	14	200 U/kg, 5 days/wk	+1.9
Lavey and Dempsey, 1993 (7)	Malignant tumor above diaphragm	20	200 U/kg/day for 2 weeks	+3.2
Dusenbery *et al.*, 1994 (6)	Cervix	15	200 U/kg/day, 5 days/wk for 10 doses, then 3 days/wk	+3.1
Throuvalas *et al.*, 2000 (9)	Cervix, bladder	28	10,000 U, 5 days/wk	+1.0

Abbreviations: EPO = erythropoietin; Hb = hemoglobin.

how much change would be necessary to shift the comparison of costs from the situation in which EPO is more expensive toward a situation in which EPO is less expensive. A 100-fold increase in the risk associated with possible HIV, HCV, or HBV infection was insufficient to render the transfusion cost projection higher than the cost of EPO use. However, an 80% reduction in the direct cost of EPO or a fourfold escalation of the price of transfusions would render EPO less costly than transfusions in the conditions studied.

DISCUSSION

The results of the present study indicate that to maintain Hb levels during pelvic RT and weekly cisplatin chemotherapy for cervical cancer, it is approximately four times more expensive to use EPO than RBC transfusions. The incremental added cost of using EPO instead of RBC transfusions was projected to be approximately $3000.

Medical practitioners of all subspecialties are now entreated not only to provide individual patients state-of-the-art care but also to be responsible for the efficient allocation of fiscal resources in their disease management efforts. Challenges arise when novel, albeit expensive, technologies promise appealing clinical effects. Physicians must then judge whether the putative advantages of the new device or pharmaceutical agent warrant the added expenditure. The cost-effectiveness of adding chemotherapy to RT for cervical cancer, for example, has recently been analyzed (19).

For the case of EPO use during RT to correct or prevent anemia, at least 4 studies have demonstrated that EPO can raise the Hb level of patients receiving RT for a variety of malignancies (6–9). Table 3 includes details of the EPO dosage and clinical outcome in those studies. Perhaps not surprisingly, the strongest effect on erythropoiesis was observed in the study reported by Lavey and Dempsey (7) in which patients were receiving RT to sites other than the pelvic bone marrow. A more modest effect was observed in the study by Throuvalas *et al.* (9) in which patients received not only pelvic RT but also concurrent chemotherapy.

Our observation that EPO is several times more expensive than transfusions in the conditions studied is consistent with other cost comparisons of EPO and transfusion. Table 4 includes all other known published reports comparing the cost of transfusion with the cost of EPO for a variety of indications (20–26). The present study is the only one that includes RT as a component of treatment; the other studies involve either chemotherapy-related anemia or else anemia related to nonmalignant disease. The singular exception to

Table 4. Cost analyses comparing blood transfusion with EPO for management of anemia in selected indications to achieve equivalent clinical outcome

Study	Anemia cause	EPO dose and duration	Cost (U.S.$)	
			EPO	Transfusions
Cantor *et al.*, 1993 (20)	AIDS therapy*	Not stated; maximum $8500/yr cost	13,684	4588
Ohls *et al.*, 1995 (21)	Prematurity	200 U/kg/day for 2 weeks	129	255
Fain *et al.*, 1995 (22)	Prematurity	100 U/kg 5 days/wk for 6 weeks	1326	721
Sheffield *et al.*, 1997 (23)	Chemotherapy†	150 U/kg, 3 days/wk‡	12,971	4481
Barosi *et al.*, 1998 (24)	Chemotherapy§	150 U/kg 3 days/wk for 16 wk	4440	426
Ortega *et al.*, 1998 (25)	Chemotherapy	150 U/kg 3 days/wk for 12 wk	3700	583
Meadowcroft *et al.*, 1998 (26)	Chemotherapy‖	150 U/kg 3 days/wk for 4 cycles¶	6483	169
Present study	Chemo-RT, cervix cancer	10,000 U 5 days/wk for 6 wk	3869	996

* Zidovudine.
† Hodgkin's disease, breast cancer, non–small cell lung cancer.
‡ If no response after 6 weeks, dose escalated to 300 U/Kg, 24 weeks total.
§ Lung cancer, genitourinary cancer, gynecologic cancer, breast cancer, lymphoma, multiple myeloma.
‖ Breast cancer.
¶ Doxorubicin and cyclophosphamide, with or without fluorouracil.
Abbreviations: EPO = erythropoietin; AIDS = acquired immunodeficiency syndrome; RT = radiotherapy.

the observed trend whereby EPO is more costly than transfusion is the report by Ohls *et al.* (21) analyzing EPO usage in premature infants. However, it should be noted that in their study, incorporating an EPO dose proportional to body mass, the total quantity of EPO given to each patient was very low, because a premature infant's body mass is very low.

It has not been demonstrated that the added expenditure associated with EPO use provides clinical benefit beyond what is achieved by RBC transfusion. Prior reports have not shown a clear quality-of-life benefit with EPO over transfusion for patients receiving RT (6, 8). However, although direct comparisons of any effects on intratumoral hypoxia have not been reported, it is possible that EPO might be advantageous in this regard. For instance, conditions present within hypoxic regions of tumors have been shown to cause an adverse effect on RBC deformability, which can impede blood flow through tumors (27). EPO might mitigate this effect by releasing a population of highly deformable RBCs, as it promotes the peripheral distribution of reticulocytes (28). Furthermore, transfused blood is expected to contain reduced levels of 2,3-DPG and a corresponding shift in Hb–oxygen affinity toward conditions wherein oxygen release is inhibited (29), although any adverse effect is likely transient. Apropos of this issue, ongoing clinical trials involving the agent RSR13, a synthetic allosteric modifier of hemoglobin, are designed to enhance tumor oxygen delivery by reducing Hb–oxygen affinity (30).

Transfusion-related cost estimates from the current analysis would be modified by either changes in the risk of transfusion-related complications or changes in the fees for screening and preparing blood for transfusion. In particular, the risks of contracting HIV and HCV from blood screened by nucleic amplification testing are likely even lower than the more conservative risk estimates applied in the present analysis. Not yet universally applied clinically, nucleic amplification testing is more sensitive than the current Food and Drug Administration–licensed methods and is capable of detecting serologically silent HCV and HIV in blood donors (31). As the number of individuals who become infected with HIV, HCV, and HBV by transfusion declines, other rare transfusion-related complications are being recognized. Notably, the risk of bacterial contamination of blood products, estimated to be 1 in 500,000/U of RBC and as high as 1 in 1000 for platelets, is now considered the most serious transfusion-transmitted disease, leading in some cases to major morbidity or mortality (32). Another issue gaining attention recently is the possible immunocompromising effect of transfusion, presumed to be mediated by white blood cells. Contaminating white blood cells are suspected to increase susceptibility to postoperative infection and other sequelae of diminished immune system function. Leukoreduction to remove white blood cells from all types of transfusion has been proposed as a solution (33). As the effort to minimize all transfusion risks continues, the cost of blood transfusions will likely rise. Universal nucleic amplification testing and other advances in pathogen identification and inactivation would also add expense. Leukoreduction alone could increase the cost of 1 U of RBCs by as much as 40% (34, 35).

Ultimately, physicians' selection of either transfusion or EPO for control of Hb levels during RT should be influenced not only by the cost differential in their region but also by other important considerations relating to the individual clinical situation. EPO is not appropriate for patients unwilling or unable to be compliant with frequent EPO injections; these individuals are well served with transfusions. On the other hand, blood banks frequently have a limited supply of uncommon ABO/Rh types, and these resources are generally reserved for emergencies in facilities in which organ transplants, trauma surgery, and other major procedures are routinely performed. Nevertheless, for most patients transfusions are an effective and appealingly less expensive option.

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