The Costs and Cost-Effectiveness of Unrelated Donor Bone Marrow Transplantation for Chronic Phase Chronic Myelogenous Leukemia

By Stephanie J. Lee, Claudio Anasetti, Karen M. Kuntz, Jonathan Patten, Joseph H. Antin, and Jane C. Weeks

Unrelated donor transplantation prolongs survival in some patients with chronic myelogenous leukemia (CML) in chronic phase. However, there are growing concerns about the intensive resources required for this procedure given health care budget constraints. To address this issue, we conducted a study of the costs and cost-effectiveness of unrelated donor transplantation for chronic phase CML. The costs of transplantation were derived from 157 patients from the Brigham and Women's Hospital (BWH) and the Fred Hutchinson Cancer Research Center (FHCRC). Estimates of the effectiveness of transplantation were taken from our previous work using data from the International Bone Marrow Transplant Registry and the National Marrow Donor Program. The median cost of the first 6 months of care including donor identification, marrow collection, patient hospitalization, and posttransplant care was $196,200. Mean costs for patients surviving beyond 6 months posttransplant were significantly lower than for patients dying within that period ($189,700 vs $211,000, respectively, P < .03). Posttransplant follow-up costs were high for months 6 to 12, then decreased. The incremental cost-effectiveness of transplantation within 1 year of diagnosis versus interferon therapy without transplant in the base case of a 35-year-old patient was $51,800/quality-adjusted life year (QALY) gained. Sensitivity analysis showed that most ratios were between $50,000 to $100,000/QALY or within the intermediate zone of acceptable cost-effectiveness ratios.

A PROXIMATELY 4,300 people are diagnosed with chronic myelogenous leukemia (CML) annually in the United States. Allogeneic stem cell transplantation is the only proven curative therapy, but patient age, comorbid disease, and inability to identify a donor limit this option to a minority of patients. It has been estimated that 35% of patients with CML under the age of 55 years will undergo allogeneic transplantation in the United States. Despite the relatively small number of individuals undergoing transplantation for this indication, the high morbidity of the procedure and the fact that only a subset of transplanted patients survives long-term have led many to question whether the benefits of transplantation justify the costs. When unrelated donors are required, the donor identification process raises costs, while higher morbidity and mortality lower benefits relative to related-donor transplantation.

Calculation of cost-effectiveness ratios using standardized methods facilitates judgments about whether the benefits of a medical intervention are sufficient to justify the costs. The common measure of dollars per quality-adjusted life year (QALY) gained used in cost-effectiveness ratios allows comparisons among diverse medical interventions including those that improve quality of life and those that extend length of life, and very high-cost, life-saving procedures applied to few individuals and low-cost, modest benefit ones applied to large populations. Rough guidelines for acceptable cost-effectiveness ratios have been suggested based on current budgetary constraints and demonstrated societal spending choices. In general, interventions available at less than $50,000 per QALY have been considered cost-effective. A cost-effectiveness ratio of greater than $100,000 per QALY is not considered cost-effective relative to other interventions. Cost-effectiveness ratios between $50,000 to $100,000 per QALY are intermediate.

This study was undertaken to evaluate the costs and cost-effectiveness of non-T-cell depleted unrelated donor transplantation for chronic phase CML. The analysis considers all phases of transplantation: donor identification, donor and patient evaluation, stem cell harvest, hospitalization for transplant, posttransplant outpatient care and medications, and readmissions to the hospital. Primary cost data were obtained from a large cohort of patients transplanted at two major medical centers. Based on our previous study of the effectiveness of unrelated donor transplantation for chronic phase CML, we were able to calculate a cost-effectiveness ratio for this procedure and examine sensitivity to a variety of assumptions.

MATERIALS AND METHODS

Cost data sources—Transplantation. Sequential cohorts of patients with chronic phase CML undergoing transplantation from fully matched or one antigen mismatched unrelated donors at two institutions provided the primary cost data. Class I A and B antigens were typed serologically, while class II DRB1 allele typing used either serologic or molecular techniques. The first group of 49 patients was transplanted at the Brigham and Women’s Hospital (BWH), Boston, MA between June 1991 and December 1996. The second cohort of 108 patients was transplanted between January 1992 and April 1996 at the Fred Hutchinson Cancer Research Center (FHCRC), Seattle, WA. Patients received cyclophosphamide and total body irradiation (12 to 14 Gy) with or without high dose cytarabine. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and methotrexate with or without steroids. Some patients were treated on research protocols, which may have increased costs. However, we were not able to separate protocol costs from other clinically indicated studies and procedures, or adjust costs for clinical effects resulting from these protocols.

All medical costs were obtained from the accounting systems at the

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Submitted March 26, 1998; accepted July 23, 1998.

Supported in part by a Health Services Research Fellowship from the Agency for Health Care Policy and Research and National Institutes of Health Grant No. CA75267-01.

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0006-4971/98/9211-0013$3.00/0


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BWH and FHCRC. Costs incurred before October 1992 at the BWH were calculated based on the charges adjusted by the institutional aggregate ratio of costs to charges (RCC). After October 1992, charges were converted to costs using departmental RCC adjustments. The institutional RCC was used for all FHCRC data because departmental figures were not available. Professional fees were not available at either institution and are not included in this analysis. All costs were adjusted to 1996 dollars using the medical care component of the consumer price index.

Costs were divided into peritransplant (within 1 month before hospitalization for transplantation until 6 months postmarrow infusion) and posttransplant (divided into 6-month intervals, including both inpatient and outpatient care). Costs of donor identification, all necessary pretransplant testing for patient and donor, and marrow collection costs were included in the peritransplant period regardless of when they occurred. Two patients in the Fred Hutchinson cohort underwent second stem cell infusion during their initial transplant hospitalization. All costs for these procedures were included. Two additional Fred Hutchinson patients underwent second transplantation more than 6 months after their initial transplant. These second transplants were considered to be part of the initial Fred Hutchinson hospitalization costs after adjustment for year of transplant to assure inclusion in the analysis (because only Brigham and Women’s patients were used to calculate posttransplant follow-up costs). No Brigham and Women’s Hospital patient received additional stem cell infusions or adoptive immunotherapy, underwent second transplant, or relapsed.

Because 90% of patients transplanted at FHCRC live outside the local Seattle area and were returned to the care of their local physicians after 100 days, cost data available from this site underestimate true peritransplant costs. Using BWH data, we examined the contribution of costs occurring between 3 to 6 months to total peritransplant costs and found that they represented only 3.8% of the total. Thus, no adjustments were made for loss of information between 100 days and 6 months for the Fred Hutchinson patients. Costs during the peritransplant period (~1 to 6 months) did not differ between the institutions and were pooled.

Because most Fred Hutchinson patients left the Seattle area after 100 days, long-term cost data were not available. Thus, only patients from the BWH were used to determine posttransplant care costs because detailed information was available. All inpatient and outpatient activity through September 1, 1997 was captured from the hospital accounting system and converted to costs using departmental RCCs. In addition, the charts of all BWH patients were reviewed to assure inclusion of hospitalizations outside of the area, outpatient medication usage, and other procedures not captured in the institutional accounting system. When patients were hospitalized at outside institutions and bills were not available, length of stay was multiplied by the approximate daily inpatient cost for other patients readmitted to the BWH ($1,500/d). Outpatient medication costs were calculated using the average wholesale price published in the 1997 Red Book. When available, prices quoted for the Health Care Financing Agency or generic brands were used. A pharmacy dispensing fee of $2.50/mo was added for each medication. The cost of outpatient dialysis was not available from patient bills and was therefore assigned the inpatient procedure dialysis cost of $500/d.

Costs were calculated for 6-month intervals based on the number of individuals alive at the start of each interval; the median costs for the intervals were relatively stable. A highly aberrant cost (a single hospital admission 3 years posttransplant costing $100,000) was included in the base case evaluation and its influence tested in sensitivity analysis.

Cost data sources—Nontransplant management of CML. The costs of CML care without transplantation were divided into two categories: outpatient medical therapy for chronic phase CML and inpatient induction therapy for blast crisis. We estimated that patients would require maintenance doses of either 5 million units/m² (assuming a body surface area of 1.8 m²) of α-interferon three times per week ($14,470/year) or 1,000 mg of hydroxyurea a day ($932/yr) to maintain control of counts. Only 50% of patients beginning α-interferon were assumed to continue this medication after 6 months, while the rest returned to hydroxyurea treatment. Medication costs were estimated from doses in the literature and the average wholesale prices as listed in the Red Book. Patients were estimated to have one moderate-complexity visit every other month ($78) in conjunction with phlebotomy ($2.75) and a complete blood count ($5.40). No other medication or medical care costs were assumed during the outpatient phase.

Inpatient costs for induction chemotherapy were collected from the BWH accounting system for eight patients treated for 10 episodes of CML in blast crisis with a variety of chemotherapy regimens between June 1992 and June 1997. Costs were calculated from charges using methods identical to those used for transplant costs. In the absence of published estimates, we assumed that 100% of untransplanted patients would eventually enter blast crisis unless they died of a cause unrelated to their CML, and 50% of patients entering blast crisis would undergo one induction chemotherapy cycle in an attempt to reenter chronic phase. No other terminal care costs were included.

Perspective of the cost analysis. A modified societal perspective was adopted for the cost analysis. Although societal costs should also include nonmedical items such as transportation to the hospital and caregiver time, given the retrospective nature of the analysis, no attempt was made to enumerate and include these costs. In addition, medical services provided within the home could not be captured due to lack of documentation in the hospital accounting system or the medical record.

Whereas the charges appearing on hospital bills reflect market influences and payments often vary with contract negotiations, costs are estimates of the actual resources used to provide the service. All monetary figures presented in this report refer to costs, which are usually lower than charges.

The Markov model. A Markov model is an analytic framework, which tracks the clinical events occurring in a hypothetical cohort of patients under various scenarios. The analyst sets the key parameters of the model based on clinical information and reasonable assumptions. The model can then be used to test the effect of changes in assumptions on the final outcome of the cohort.

The costs were incorporated into our decision analysis Markov model, which calculates discounted, quality-adjusted life expectancies of newly diagnosed CML patients based on their age, time from diagnosis to transplant, and whether they choose transplant or nontransplant therapy. The base case was considered to be a 35-year-old patient. We compared transplantation within the first year after diagnosis with α-interferon or hydroxyurea therapy. The outcomes of α-interferon and hydroxyurea treatment were represented by results of a meta-analysis of seven randomized trials analyzed on an intention-to-treat basis. Survival beyond 5 years was modeled using the annual death rates for later years as presented in the paper. A discount rate of 3% per year was used for both costs and life years, and utilities of 0.979 for life without chronic GVHD, and 0.90 for life with chronic GVHD, respectively, were assumed. These utilities were derived from physicians using the standard gamble methodology as previously described. For the purpose of this analysis, we assumed a utility of 1.0 for either α-interferon or hydroxyurea therapy and tested this assumption in sensitivity analyses.

We calculated an incremental cost-effectiveness ratio, which is the difference in costs divided by the difference in effectiveness between a given therapy and the next best option. This is an appropriate value to use when deciding between mutually exclusive therapies. Note that this value is different than simply the costs of a program divided by its benefits.

Sensitivity analysis. Sensitivity analyses were performed on key variables including cost estimates, patient age, discount rate, utilities, handling of aberrantly high posttransplant hospitalizations, and long-
term medical costs more than 5 years posttransplant. Ranges for testing were identified from the medical literature and the recommendations of the Panel on Cost-Effectiveness in Health and Medicine.15

Statistical methods. Costs were compared using the Wilcoxon Rank Sum test. Multiple linear regression was used to assess the association between peritransplant costs and patient age, patient gender, whether a patient was mismatched, site, length of stay during the transplant hospitalization and whether a patient died during the transplant hospitalization or after hospital discharge, but before 6 months. A stepwise forward selection process was used to determine variables significant at \( P < .05 \).

RESULTS

Patient characteristics. The characteristics of patients from the FHCRC and the BWH are shown in Table 1 and are similar to those of the registry cohort used to calculate effectiveness. Three-year overall survival was similar for the combined FHCRC/BWH cohort transplanted at different intervals from diagnosis (59%) and used in the cost analysis, and registry patients transplanted within 1 year of diagnosis (58%) used to calculate effectiveness. The overall survival for the 45 FHCRC/BWH patients who were 50 years old or less and transplanted from fully matched unrelated donors within 1 year of diagnosis was 77% at 3 years (median follow-up, 3.16 years).

Costs of Unrelated Donor (URD) transplantation for CML. Median costs through 6 months posttransplant were not significantly different between the two institutions and were pooled (FHCRC $173,300; range, $85,000 to $462,400 v BWH $193,200; range, $99,100 to $331,300, \( P = .27 \)). Room and board accounted for 30% to 39% of costs, while pharmacy represented 21% to 24% of costs. The majority of other costs were attributable to donor identification and marrow procurement, diagnostic studies, and blood bank. Mean peritransplant costs (including donor identification and harvest) were $196,200 for the combined cohort (median $178,500; range, $85,000 to $462,400). In multivariate modeling, the most significant predictors of costs within the first 6 months were initial hospital length of stay (partial \( r^2 = .33, P = .0001 \)) and death (partial \( r^2 = .04, P = .0025 \)). Factors identifiable before transplantation (site, patient age, patient gender, degree of matching, time from diagnosis to transplant) were not found to be significantly predictive at \( P < .05 \). Conclusions were unchanged if the logarithm of costs was modeled. Patients who survived to hospital discharge, but died before 6 months, were the most costly because of the high costs of rehospitalization.

Posttransplant care costs remained high during months 6 to 18 posttransplant, then decreased and plateaued except for a single hospitalization 3 years after transplantation, which cost $100,000 (Table 2). The effect of alternative approaches to handling this aberrant value was tested in sensitivity analysis. For the base case, an average of costs over the period of 18 to 54 months was calculated and the mean value of $6,900/6 mo was incorporated into the model during this time period. Beyond 54 months, cost data were not available and $5,900/6 mo (the average cost through 54 months excluding the outlier) was entered into the model for all surviving patients.

Patients dying within 6 months of transplantation (n = 48) were significantly more costly in the first 6 months than those surviving (n = 109) beyond 6 months ($211,000 v $189,700, respectively, \( P = .03 \)). Thus, we entered separate costs into the model for patients who did and did not survive beyond 6 months. Although it has been noted in the literature that patients use more resources just before their deaths of other diseases, the small number of deaths beyond the 6-month period did not allow us to evaluate this or incorporate differential costs into the model.16

Cost-effectiveness analysis. The base case was defined as a 35-year-old patient transplanted within 1 year of diagnosis. This scenario was compared with one in which the same patient elected interferon or hydroxyurea therapy. Discounted lifetime costs of transplantation were calculated to be $333,600, while the cost of interferon therapy was $61,800 and hydroxyurea therapy, $31,400. The model calculated that a 35-year-old
patient transplanted within 1 year of diagnosis would attain 9.95 discounted, quality-adjusted life years (QALYs), while a patient treated with interferon would have 4.70 QALYs. Therefore, the incremental cost-effectiveness ratio of early bone marrow transplantation (BMT) versus interferon is $51,800/QALY. When early BMT is compared with hydroxyurea therapy, the incremental cost-effectiveness ratio is $55,500/QALY.

Sensitivity analysis. In sensitivity analysis, which looks at the effects of different modeling assumptions, the cost-effectiveness ratios for early BMT versus α-interferon ranged from $32,600/QALY to $126,800/QALY, although most fell within the range of $50,000 to $100,000/QALY (Table 3). Variables such as patient age that influenced the effectiveness of transplantation had the greatest influence on the cost-effectiveness ratio. Age at transplant of 25 years rather than 35 lowered the cost-effectiveness ratio to $43,200/QALY, while the ratio for a 45-year-old patient was high at $126,800/QALY. Using the α-interferon arm of the Guilhot et al study17 instead of the meta-analysis results14 in the model increased the cost-effectiveness ratio to $86,100/QALY. When we used the survival curve of the 45 patients in the FHCRC/BWH cost cohort who were 50 years old or less at the time of transplant, received marrow from 6 of 6 matched donors and were transplanted less than 1 year from the time of diagnosis (3-year overall survival 77%, median follow-up, 3.16 years), the cost-effectiveness ratio was $42,200/QALY.

If we assume that the quality of life of patients treated with interferon is the same as patients with chronic GVHD (0.9), the incremental cost-effectiveness ratio would be $49,500/QALY.

**Table 3. Incremental Cost-Effectiveness of Unrelated Donor Transplantation for CML Compared With Interferon-α**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>ΔC (1996$)</th>
<th>ΔE (QALY)</th>
<th>Incremental C/E*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline assumptions†</td>
<td>271,800</td>
<td>5.25</td>
<td>51,800</td>
</tr>
<tr>
<td>Costs</td>
<td>333,600</td>
<td>5.25</td>
<td>63,500</td>
</tr>
<tr>
<td>80% treated for blast crisis</td>
<td>257,000</td>
<td>5.25</td>
<td>48,900</td>
</tr>
<tr>
<td>BMT costs $100,000</td>
<td>177,100</td>
<td>5.25</td>
<td>33,700</td>
</tr>
<tr>
<td>BMT costs $300,000</td>
<td>377,000</td>
<td>5.25</td>
<td>71,800</td>
</tr>
<tr>
<td>Continue follow-up at $6,900/6 mo</td>
<td>287,500</td>
<td>5.25</td>
<td>54,800</td>
</tr>
<tr>
<td>Effectiveness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age = 25 yr</td>
<td>291,500</td>
<td>6.75</td>
<td>43,200</td>
</tr>
<tr>
<td>Age = 45 yr</td>
<td>227,900</td>
<td>1.80</td>
<td>126,800</td>
</tr>
<tr>
<td>Survival of FHCRC/BWH complete cohort, N = 157</td>
<td>263,400</td>
<td>4.55</td>
<td>57,900</td>
</tr>
<tr>
<td>Survival of FHCRC/BWH best risk cohort, N = 45‡</td>
<td>335,400</td>
<td>7.95</td>
<td>42,200</td>
</tr>
<tr>
<td>Utility without cGVHD = 0.9, utility with cGVHD = 0.7</td>
<td>271,800</td>
<td>3.76</td>
<td>72,300</td>
</tr>
<tr>
<td>Utility of IFN = 0.9</td>
<td>271,800</td>
<td>5.49</td>
<td>49,500</td>
</tr>
<tr>
<td>Costs and effectiveness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discount rate 0%/yr</td>
<td>338,200</td>
<td>10.38</td>
<td>32,600</td>
</tr>
<tr>
<td>Discount rate 5%/yr</td>
<td>249,200</td>
<td>3.52</td>
<td>70,900</td>
</tr>
<tr>
<td>Discount rate 7%/yr</td>
<td>235,000</td>
<td>2.43</td>
<td>96,800</td>
</tr>
</tbody>
</table>

ΔC, difference in total lifetime discounted costs between transplant and nontransplant treatment; ΔE, difference in effectiveness between transplant and nontransplant therapy; Incremental C/E, incremental cost-effectiveness ratio of transplant and nontransplant therapy, in dollars per quality-adjusted life year; utilities, quality of life adjustments; discount rate, annual adjustment applied to both costs and benefits.

Abbreviations: CML, chronic myelogenous leukemia; BMT, bone marrow transplantation; FHCRC, Fred Hutchinson Cancer Research Center; BWH, Brigham and Women’s Hospital; cGVHD, chronic graft-versus-host disease; IFN, α-interferon.

*$/QALY.
†35-year-old patient transplanted within 1 year of diagnosis for CML in chronic phase versus α-interferon therapy.
‡Age ≥50 years old, matched donor, transplanted within 1 year of diagnosis.

DISCUSSION

Our results highlight that unrelated donor transplantation for CML is expensive in absolute costs, but because it prolongs life substantially for some patients, the ratio of costs to effectiveness is in the range of other well-accepted medical interventions. Compared with α-interferon therapy, we estimate that unrelated donor transplantation costs $271,800 more, but results in an average of 5.25 more quality-adjusted life years for a 35-year-old patient. Thus the incremental cost-effectiveness ratio is $51,800/QALY. Sensitivity analysis showed that this estimate is fairly robust; when model parameter estimates were varied through clinically realistic ranges, the cost-effectiveness ratio generally remained between $50,000/QALY and $100,000/QALY.

Previous studies have shown that the short-term cost of allogeneic transplantation from related donors ranges from $100,000 to $200,000.18-25 We found the costs of care in the first 6 months after unrelated donor transplantation to be $196,200, higher than most estimates for related donor transplantation, but not dramatically so. This likely reflects the fact that while patients undergoing unrelated donor transplantation have higher morbidity and thus costs, many of the initial expenses are expected to be the same, including costs of inpatient hospitalization and treatment of acute posttransplant complications.

The cost-effectiveness ratio of unrelated donor transplantation for CML may be compared with that of other medical interventions.26,27 While our base case ratio of $51,800/QALY is higher than other procedures such as cervical cancer screening in an elderly population,28 it is in the same range as other commonly performed procedures such as renal dialysis29 and more favorable than some pharmaceuticals such as the newer antihypertensive agents.30 Therefore, our results do not support the concern that the costs of unrelated donor transplantation for CML are not justified by the benefits.

We chose to model a 35-year-old patient as our base case because this represents the median age at transplant. We also focused on unrelated donor transplantation because we expected the costs to be higher and the effectiveness lower than related donor transplantation; if unrelated donor transplantation is cost-effective, then one would expect the cost-effectiveness ratio for related donor transplantation to be even more favorable. Although we are not aware of any reports of the cost-effectiveness of related donor transplantation for CML,
published ratios for acute myelogenous leukemia range from $15,300 to $29,000 per life year saved (adjusted to 1996 dollars).\textsuperscript{19,22}

Several limitations to this study must be noted. First, the efficacy results were derived from modeling, as no randomized trials of transplant versus nontransplant therapy have been performed. More recent changes in transplantation practice, such as better HLA matching or approaches to GVHD, are not reflected in this cohort. Second, the cost data were retrospective and accrued over a number of years at only two institutions. They do not include the costs of establishing the unrelated donor registry or donor searches for patients unable to locate a donor. Inclusion of professional fees, which are likely higher in the transplant arm than the nontransplant arm, would be expected to raise the net cost of the transplantation strategy. Third, although we had follow-up cost data until 5 years posttransplant, we do not know if those cured of their malignancy by transplantation will have more late medical complications and costs than the average population. Fourth, we note that both nontransplant\textsuperscript{17} and transplant\textsuperscript{9} therapy are improving and that cost-effectiveness ratios will need to be continually reevaluated in light of changes in costs and effectiveness.

On the other hand, many assumptions in this analysis favor nontransplant therapy. For example, we assumed that only 50% of patients entering blast crisis would undergo induction therapy. We also excluded several costs, which would be expected to improve the cost-effectiveness ratio of transplantation, such as cytogenetic studies and palliative care for patients electing nontransplant therapy. Therefore, the cost-effectiveness ratio of transplantation may well be an overestimate.

Thus, unrelated donor transplantation is costly, but the high degree of effectiveness in appropriate populations results in a cost-effectiveness ratio comparable to that of other accepted medical interventions used in the prevention, screening or treatment of both malignant and nonmalignant disease. Furthermore, if transplant costs can be lowered while health outcomes improve, the cost-effectiveness ratio of unrelated donor transplantation will become more favorable than shown in this analysis.

ACKNOWLEDGMENT

We thank Dr Fred Appelbaum for review of the manuscript and helpful comments. Victoria Doroshenko was helpful in providing cost data. The International Bone Marrow Transplant Registry and the National Marrow Donor Program provided the data used to calculate the effectiveness of unrelated donor transplantation.

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