Peripheral blood stem cells (PBSCs) and bone marrow (BM) hematopoietic stem cells represent therapeutic alternatives in allogeneic hematopoietic cell transplantation. Randomized controlled trials and an individual patient data meta-analysis (IPDMA) have demonstrated a decreased risk of disease relapse and an increased risk of acute and chronic graft-versus-host disease (aGVHD, cGVHD) in patients receiving PBSCs compared with those receiving BM stem cells. Decision modeling provides quantitative integration of the risks and benefits associated with these alternative treatments, incorporates survival discounts for lower quality of life in patients with aGVHD or cGVHD and post-transplantation relapse, and allows sensitivity analyses for all model assumptions. We have constructed an externally validated Markov model to represent and analyze the decision to use PBSC or BM, estimating post-transplantation state transition probabilities (eg, GVHD and relapse) and quality-of-life discounts from the IPDMA and relevant literature; importantly, this IPDMA synthesized data from primarily adult patients treated with myeloablative (MA) conditioning regimens with T cell–replete matched sibling donors. In this setting, the model demonstrates the superiority of PBSC over BM in both overall and quality-adjusted life expectancy, with a 7-month advantage for PBSC. Sensitivity analyses support this conclusion through a range of values for each variable supported by the IPDMA and quality-of-life discounts, as supported by the literature. However, BM is the optimal strategy in conditions in which the 1-year relapse probability is < 5%. PBSC is the optimal stem cell source in terms of both overall and quality-adjusted life expectancy, except in conditions with a very low relapse probability, in which BM provides optimal outcomes.


KEY WORDS: Peripheral blood mobilized stem cells, Bone marrow stem cells, Allogeneic hematopoietic cell transplantation, Decision analysis, Markov model

INTRODUCTION

Historically, hematopoietic stem cells for autologous and allogeneic transplantation to treat hematologic malignancies have been obtained by bone marrow (BM) harvest. However, these stem cells are increasingly obtained through mobilization and collection from the peripheral blood (PB) [1-5]. A review of current trends indicates that most allogeneic stem cell transplantations are performed using PB stem cells (PBSCs) [6]. There are important differences in the composition of these stem cell products, most notably in terms of absolute CD34+ cell count and donor T cell content [7-17]. Accordingly, there is great interest in investigating the effect of the hematopoietic stem cell source on important outcomes in transplantation. Numerous randomized controlled trials have compared BM-harvested hematopoietic stem cells and PBSCs and reached disparate conclusions [18-28].

A group of investigators known as the Stem Cell Trialists set out to examine and synthesize the totality of evidence in an individual patient data meta-analysis (IPDMA). In total, they examined data on 1,111 patients from 9 randomized controlled trials that met the inclusion criteria for this analysis. In primarily adult patients treated with myeloablative (MA)
conditioning regimens and T cell–replete matched sibling allografts, transplantation with PBSCs led to faster neutrophil and platelet engraftment, a significant increase in the development of grade III/IV acute graft-versus-host disease (aGVHD) as well as extensive and overall chronic GVHD (cGVHD), and decreased relapse in both late-stage and early-stage disease compared with BM. Non-relapse mortality (NRM) did not differ between the 2 groups. Overall survival (OS) and disease-free survival (DFS) were significantly better in the PBSC transplantation (PBSCT) group in patients with high-risk disease [29].

Decision analysis is concerned with analyzing and representing outcome data to recommend a course of action that provides the optimal outcome, such as optimal overall life expectancy or quality-adjusted life expectancy (QALE). Although physicians intuitively evaluate outcome data and make decisions, decision analysis allows for an explicit, quantitative integration of all data on the risks and benefits associated with competing treatment alternatives. A decision model consists of health states, such as perfect health, illness, and death. The state transition probabilities represent the likelihood of proceeding from one state to the next in the model. Finally, health state utilities are the value assigned to each state, ranging from 0 to 1, with 0 representing death and 1 representing perfect health. We used the Markov state transition model, because the decision of BM transplantation (BMT) versus PBSCT involves risk over time, and multiple complicating events can occur. We have designed a Markov state transition model to represent the decision of BMT versus PBSCT, estimating state transition probabilities and assigning expected utilities based on the foregoing meta-analysis and, where indicated, examination of the pertinent literature [30,31]. This decision analysis offers novel information regarding the impact of stem cell source on transplantation outcome by quantitatively integrating the competing risks and benefits of PBSC and BM to recommend a strategy for optimal outcome. In addition, incorporation of health state utilities allows a comparison of QALE among these alternatives. Finally, sensitivity analyses examine a range of potential values for each variable in the model, such as relapse or cGVHD, providing insight into the conditions under which these conclusions hold true.

**METHODS AND ANALYSIS**

We constructed a Markov decision model to represent the decision of PBSCT versus BMT using TreeAge Pro 2008 software (see Supplementary Appendix A). Following a decision node of PBSCT versus BMT, cloned Markov trees follow with a structure consisting of the following distinct health states important to hematopoietic stem cell transplantation: transplantation, engraftment failure, aGVHD, cGVHD, relapse, on immunosuppressive therapy (IST), off IST, death from 

<table>
<thead>
<tr>
<th>Probability</th>
<th>Data Source</th>
<th>Estimate (PBSCT)</th>
<th>Adjusted for Month Cycle Length (PBSCT)</th>
<th>Estimate (BMT)</th>
<th>Adjusted for Month Cycle Length (BMT)</th>
<th>Range for Sensitivity Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engraftment failure</td>
<td>Meta-analysis</td>
<td>0.03</td>
<td>0.03</td>
<td>0.05</td>
<td>0.05</td>
<td>0.01-0.08</td>
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<td>aGVHD</td>
<td>Meta-analysis</td>
<td>0.412</td>
<td>0.137</td>
<td>0.379</td>
<td>0.126</td>
<td>0.12-0.8</td>
</tr>
<tr>
<td>Death from aGVHD</td>
<td>Meta-analysis</td>
<td>0.153</td>
<td>0.01275</td>
<td>0.156</td>
<td>0.013</td>
<td>0-0.3</td>
</tr>
<tr>
<td>Relapse, year 1</td>
<td>Meta-analysis</td>
<td>0.065</td>
<td>0.05</td>
<td>0.069</td>
<td>0.0058</td>
<td>0.03-0.12</td>
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<tr>
<td>Relapse, year 2</td>
<td>Meta-analysis</td>
<td>0.0143</td>
<td>0.0012</td>
<td>0.053</td>
<td>0.0044</td>
<td>0.005-0.08</td>
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<td>Treatment success aGVHD</td>
<td>Literature</td>
<td>0.4</td>
<td>0.067</td>
<td>0.4</td>
<td>0.067</td>
<td>0.25-0.75</td>
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<tr>
<td>cGVHD through year 1</td>
<td>Meta-analysis</td>
<td>0.59</td>
<td>0.098</td>
<td>0.45</td>
<td>0.075</td>
<td>0.05-0.7</td>
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<td>cGVHD beyond</td>
<td>Meta-analysis</td>
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<td>0.0075</td>
<td>0.08</td>
<td>0.0067</td>
<td>0.05-0.15</td>
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<tr>
<td>cGVHD complications beyond</td>
<td>Meta-analysis</td>
<td>0.4</td>
<td>0.067</td>
<td>0.25</td>
<td>0.042</td>
<td>0.1-0.5</td>
</tr>
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<td>0.125</td>
<td>0.01</td>
<td>0.05-0.2</td>
</tr>
<tr>
<td>Treatment success cGVHD</td>
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<td>0.0083</td>
<td>0.3</td>
<td>0.0083</td>
<td>0-0.7</td>
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<tr>
<td>Taper IST</td>
<td>Stewart et al. [32]</td>
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<td>0.011</td>
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<td>0.0083</td>
<td>0.05-0.3</td>
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<td>0.00375</td>
<td>0.065</td>
<td>0.0054</td>
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<td>0.01</td>
<td>0.125</td>
<td>0.01</td>
<td>0.05-0.2</td>
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<td>0.01</td>
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<td>0.20</td>
<td>0.067</td>
<td>0.09-0.39</td>
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<td>0.067</td>
<td>0.09-0.39</td>
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<td>Meta-analysis</td>
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<td>RRI*lateTRM</td>
<td>RRI*lateTRM</td>
<td>RRI*lateTRM</td>
<td>RRI: 1-5</td>
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<td>35</td>
<td>18-65</td>
<td>18-65</td>
<td>18-65</td>
</tr>
<tr>
<td>ASR mortality</td>
<td>Literature</td>
<td>estimates (see Methods)*</td>
<td>U.S. standard ASR mortality</td>
<td>0-1.0</td>
<td>U.S. standard ASR mortality</td>
<td>0-1.0</td>
</tr>
</tbody>
</table>
| aGVHD indicates acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; TRM, treatment-related mortality; IST, immunosuppressive therapy; RRI, relative risk increase; ASR, age/sex/race.

![Table 1. Probability Estimates with Data Sources](image)

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relapse, and death. Transition probabilities were estimated primarily from the Stem Cell Trialists individual patient data meta-analysis (IPDMA), and, where indicated, estimates were gathered from a search of relevant literature (see Table 1 for probability estimates). Importantly, probability estimates were adjusted to conform to a 1-month cycle length in the model. Health state utilities were estimated for calculating QALE in the quality-adjusted model. Analyses were performed using cohort analysis; this analysis includes the entire time horizon, extrapolating beyond the available data. Future discounting was not included. Modeling assumptions were tested extensively, and the model was validated externally through comparison of major outcomes predicted with those reported in the meta-analysis (see Appendix B). In addition, sensitivity analyses were performed on all transition probability estimates and health state utilities to examine the impact of a range of values for each on the reported outcome.

**Base Case Assumptions**

A base case age of 35 years was assumed in this analysis, in keeping with the age distribution of the trials represented in the IPDMA. Sensitivity analyses examined an age range of 18 to 65 years.

**State Transition Probabilities**

Here, engraftment is defined as sustained neutrophil engraftment (sustained absolute neutrophil count of 0.5 x 10^9/L), with the probability estimate obtained from the IPDMA. Engraftment failure is defined as (1-probability of engraftment). The probability of aGVHD is defined as the probability of grade II-IV aGVHD from 100-day cumulative incidence reported in the IPDMA. The probability of aGVHD complications represents the probability of grade III/IV aGVHD as reported in the IPDMA. The probability of cGVHD is estimated from that of “any-stage cGVHD” in the IPDMA; the probability of cGVHD complications is used as a distinct probability to approximate “extensive-stage cGVHD” from the IPDMA. The probability of cGVHD for PBSCT and BMT is classified as that occurring “early” (within 1 year) or “late” (beyond 1 year). The probability of treatment success for aGVHD is defined as complete resolution of aGVHD after treatment with corticosteroids, with the probability estimated at 0.4 from the literature. Treatment success for cGVHD is defined as complete resolution of cGVHD with therapy, with an estimate of 0.3 obtained from a literature review. The probability of tapering IST is modeled after Stewart et al. [32], where probability of tapering off IST at 3 years was 0.4 for BMT and 0.2 for PBSCT. The probability of treatment-related mortality (TRM) is defined as follows. Nonrelapse mortality (NRM) from the IPDMA is assumed to be comprised of mortality from GVHD (aGVHD and cGVHD) and also non-GVHD-related TRM. This NRM is classified into that occurring before and that occurring after 12 months post-transplantation. Half of the NRM through this time point is assumed to result from TRM, or early TRM. aGVHD mortality is then expressed as the product of TRM * relative risk increase (RRI). Half of the NRM occurring beyond 12 months posttransplantation is assumed to result from late TRM, with cGVHD mortality expressed as late TRM * RRI. A range of values for this RRI have been examined, given the uncertainty regarding relative contribution to NRM from GVHD and non-GVHD-related TRM. The probability of relapse is modeled after the cumulative incidence of relapse in the IPDMA for PBSCT and BMT; specifically, it is based on the overall relapse probability, whereas the range of relapse probabilities encompassed by early-stage and late-stage disease is examined in sensitivity analyses. In the IPDMA, early-stage disease included chronic myelogenous leukemia (CML) in first chronic phase, acute myelogenous leukemia (AML), and acute lymphoblastic leukemia (ALL) in first complete remission (CR1), and refractory anemia (RA)/refractory anemia with excess blasts (RAEB) myelodysplastic syndromes (MDS); conversely, late-stage disease included CML in second chronic phase, accelerated phase or blast crisis, AML or ALL either refractory or in CR2 or beyond, RAEB or in transformation subtypes of MDS, multiple myeloma (MM), Hodgkin disease (HD), non-Hodgkin lymphoma (NHL), and idiopathic myelofibrosis. To model the risk for relapse in accordance with the varying slope in the relapse curve, the probability of relapse in this model is further divided into early relapse, occurring up to 1 year post-transplantation, and late relapse, described for year 2 and then year 3 and beyond. The probability of relapse mortality is modeled after the relapse-related mortality curve in the IPDMA; relapse mortality estimates are divided into early (occurring within 1 year) and late (occurring after 1 year), to recapitulate that seen in the relapse mortality curve. For baseline age/sex/race (ASR)-based mortality, the standard ASR-based mortality table for the U.S. population from relevant literature is used; these are adjusted to adhere to the month cycle length in this model.

**Health State Utilities**

In this model, health state utilities represent the quality of life associated with each state. These health state utilities are incorporated into the quality-adjusted model to estimate QALE. Our assumptions in this model were as follows: The starting state of transplantation was assigned a utility of 1.0, which represents the starting state of optimal health. Although we have found no literature to support the assignment
of a state utility for engraftment failure, here we assumed that this would be no better than the relapse state, and assigned it a value of 0.57. We assigned a utility of 0.78 for aGVHD; although there is no direct report of aGVHD state utility in the literature, we modeled this after the utility reported by Sullivan et al. [33], who derived utilities for a wide range of health states from EQ-5D scores in a large U.S. population survey. We estimated that aGVHD would most closely approximate the conditions “hepatitis” and/or “non-infectious gastroenteritis.” We assigned a utility of 0.9 to cGVHD, based on that reported by Lee et al. [34] as derived by standard gamble methods. We assigned a utility of 0.57 to relapse based on that derived by standard gamble methods and reported by Cutler et al. [35] and Sung et al. [36]. We assigned a utility of 0.979 to on IST, which is assumed to approximate that reported for “mean utility for life without chronic graft-versus-host disease after transplantation” by Lee et al. [34]. We assigned a utility of 0.99 to off IST, assuming that the utility for this state lies between that of on IST and the starting state of transplantation. We tested these assumptions in sensitivity analyses.

Model Validation

The model structure, definitions, and assumptions were tested extensively. As an external validation, we compared our predicted outcomes with those reported in the IPDMA (see Appendix B). We compared the results generated by this model with the cumulative incidence data from the IPDMA. The outcomes predicted by this model closely approximate those from the IPDMA. Specifically, there is strong concordance between the model and the IPDMA for OS, DFS, cGVHD, relapse, and NRM. The relapse mortality generated by the model exceeds that seen in the IPDMA. In addition, aGVHD is lower in the model, reflecting a model structure that favors transition away from the aGVHD state to cGVHD, on IST, and death. Importantly, however, the model consistently produces outcomes that are qualitatively concordant with the IPDMA data.

RESULTS

Using the methods described we constructed a Markov model and populated it with probability estimates and state utilities. In the unadjusted model, assuming a base case age of 35 years, the overall predicted life expectancy was 61 months for PBSCT and 54 months for BMT (Table 2). This projected life expectancy reflects the area under the survival curve. In addition, 5-year OS was 55% for PBSCT and 46% for BMT (Figure 1). The survival curves produced by the model closely approximate those reported in the meta-analysis.

We performed sensitivity analyses to challenge the assumed transition probabilities and health state utilities in this model across a range of potential values. We first performed one-way sensitivity analyses for all transition probabilities in the unadjusted model. These consistently demonstrated intuitive relationships in which an increasing probability of an adverse variable over a range of values leads to a decreased overall life expectancy.

In all other variables examined except probability of post-transplantation relapse, PBSCT was superior to BMT throughout the entire range of anticipated values. However, there was a strong negative relationship between the probability of relapse and expected overall survival. In one-way sensitivity analyses examining the probability of relapse in BMT, PBSCT was superior in a range inclusive of the values reported

<table>
<thead>
<tr>
<th>Table 2. Survival Outcomes for PBSCT versus BMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBSCT</td>
</tr>
<tr>
<td>Overall life expectancy, months</td>
</tr>
<tr>
<td>QALE</td>
</tr>
</tbody>
</table>

PBSCT indicates peripheral blood stem cell transplantation; BMT, blood marrow transplantation; QALE, quality-adjusted life expectancy.

Figure 2. One-way sensitivity analysis examining early relapse risk in BMT in the unadjusted model (baseline value, 0.156).
DISCUSSION

Decision analysis is a powerful tool that allows the quantitative integration of all data on the risks and benefits associated with competing treatment alternatives. This approach has been used to address important clinical questions in allogeneic hematopoietic cell transplantation, including optimal strategies for unrelated donor transplantation in CML [34] and the optimal timing of allogeneic transplantation in specific MDS risk categories [35]. The results of these models have strongly influenced clinical practice. Here, we have designed a decision model to discern the impact of hematopoietic stem cell source on outcomes, and also to investigate the competing threats of cGVHD and relapse on overall life expectancy and QALE. Our Markov model strongly supports PBSCT as the optimal strategy in terms of both overall life expectancy and QALE, with an advantage of 7 months for PBSCT over BMT. In addition, one-way sensitivity analyses for all major variables support this conclusion, with PBSCT remaining the optimal strategy throughout the range of values supported by the IPDMA. Because the evidence to date appears to indicate that cGVHD in PBSCT and disease relapse in BMT appear to be competing risks, we examined these in two-way sensitivity analyses. In all of the analyses reported here, relapse emerges as a significant threat to overall life expectancy and QALE. This is clear in analyses examining the probability of relapse in BMT, in which PBSCT was superior up to very low relapse probabilities, which are not seen in the IPDMA. We also made the opposite comparisons, namely, one-way sensitivity analyses for relapse in PBSCT, as well as two-way sensitivity analyses comparing relapse in PBSCT versus cGVHD in BMT. These comparisons demonstrate that at relapse probabilities far exceeding those reported for PBSCT in the IPDMA (1-year relapse probability > 0.28), a trade-off point is reached leading to BMT as the optimal strategy.

Taken together, our results demonstrate the adverse impact of disease relapse and suggest that the superiority of PBSCT in this model is driven largely by the discrepant relapse probabilities in PBSC and BMT. They also support the finding that, despite the greater extent of cGVHD seen in PBSCT, overall life expectancy and QALE are superior in PBSCT, which is consistent with the greater mortality and worse quality of life seen in relapse compared with cGVHD. This has important implications for clinical practice, as most hematopoietic cell transplantations (HCTs) now use PBSCs rather than BM-harvested stem cells.
Our conclusions regarding the superiority of PBSCT over BMT in terms of QALE are especially robust in light of the consistency of this finding across a very broad range of potential values for each health state utility. Only at a utility < 0.18 for cGVHD did the optimal path change from PBSCT to BMT. This value is a marked decrement compared with the published estimates of health state utility associated with cGVHD, which suggest a value of 0.9 with a reference state of perfect health of 1.0 [34]. Although the literature to support the estimate of 0.9 is singular, it is unlikely that others would differ to this extent.

Besides supporting the superiority of PBSCT over BMT and demonstrating that the adverse impact of cGVHD is outweighed by the lower risk of disease relapse in both overall survival and QALE, our model has other potential applications as well. This externally validated model could be used to answer specific questions related to transplantation outcome when applied to specific disease or transplantation conditions. Of note, PBSCT remained superior throughout the range of relapse probabilities examined to encompass that reported for early-stage and late-stage disease in the IPDMA; thus, this conclusion would apply to the conditions represented therein. However, at very low 1-year relapse probabilities (ie, < .05), there is a transition point below which BMT becomes the optimal strategy for overall life expectancy and QALE. Therefore, in certain conditions with potentially very low relapse risk below this threshold (eg, nonmalignant disorders like hemoglobinopathies, RA, congenital marrow failure syndromes, acquired AA), the model supports BMT as the optimal strategy [37-41]. This shift in optimal strategy likely reflects the unopposed burden of cGVHD imposed by PBSCT in this setting. Importantly, primary data from adults with T cell–replete matched related donors informed this decision model; accordingly, whether outcomes are superior with PBSCT compared with BMT in unrelated donors or in pediatric transplantation remains unknown.

ACKNOWLEDGMENTS

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbmt.2009.07.009.

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