Allogeneic Bone Marrow Transplantation for Acute Nonlymphocytic Leukemia in First Remission


Seventy-three patients with acute nonlymphocytic leukemia in first complete remission (CR) have received allogeneic bone marrow transplantation (BMT) with non-T-lymphocyte-depleted marrow obtained from matched sibling donors. The first 36 patients received a preparative regimen consisting of cyclophosphamide, 60 mg/kg/d (days -6 and -5), and 750 cGy single-dose total-body irradiation (TBI) (day -1). Subsequently, 37 patients received cyclophosphamide 60 mg/kg/d (days -6 and -5), and 165 cGy fractionated TBI administered twice daily for a total dose of 1,320 cGy (days -4, -3, -2, and -1).

Survivors have been followed from 9 to 124 months (median, 40 months). The 61% (95% confidence interval [CI], 45% to 77%) projected disease-free survival (DFS) of 41 children <18 years old does not differ significantly from the 62% (95% CI, 49% to 73%) projected DFS of 32 adults at 84 months (P = .89). Similarly, the 15% (95% CI, 1% to 29%) projected relapse rate seen in children does not differ from the 9% (95% CI, 0% to 21%) seen in adults (P = .69).

Multivariate Cox regression analysis of presenting features demonstrates that a presenting WBC count >20,000/mm³ is associated with decreased DFS (P = .01). When compared with other French-American-British (FAB) subtypes, presentation with FAB M4 or M5 morphology is significantly associated with relapse in multivariate analysis (P = .014). Other presenting features such as preparation with single-dose or fractionated TBI, interval from diagnosis to CR or CR to BMT, donor or recipient sex, and donor or recipient cytomegalovirus serology do not correlate independently with either DFS or relapse. When included in the stepwise multivariate analysis of presenting patient features, two posttransplant events, development of grades 2 to 4 acute graft-versus-host disease (GVHD) (P < .03) and development of interstitial pneumonitis (P < .001), also correlate independently with poor DFS. Allogeneic BMT provides equivalent, prolonged DFS in both children and young adults when performed in first CR and should be considered the therapy of choice for all first CR patients under 45 years of age with a suitable donor. Continued efforts to prevent and treat acute GVHD and pneumonitis as well as efforts designed to prevent relapse in patients presenting with FAB M4 and M5 morphology should further improve outcome.

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METHODS

Patient Characteristics

Seventy-three consecutive patients in the first CR of ANLL underwent allogeneic BMT with non-T-lymphocyte-depleted matched sibling donor marrow at the University of Minnesota in the interval from November 1976 to January 1987. Analyses were performed as of October 1987. All recipients and donors or their guardians signed informed consent approved by the Committee on the Use of Human Subjects in Research at the University of Minnesota. Follow-up of survivors ranges from 9 to 124 months (median, 40 months). The recipient group consisted of 34 females and 39 males ranging in age from 1.5 to 44.6 years (median, 16.9 years). The median age of 41 recipients <18 years old was 13.3 years (range, 1.5 to 17.7 years), while that of 32 adults >18 years old was 28.6 years (range, 18.3 to 44.6 years). Patient characteristics are further described in Table 1.

Preparative Regimen and Graft-versus-Host Disease Prophylaxis

Thirty-seven recipients who received transplants before June 1983 (unique patient number [UPN] 43 to 314) were prepared for BMT with a combination of cyclophosphamide, 60 mg/kg/d intravenously (IV) (days -6 and -5) and a single midline dose of 750 cGy TBI administered at a dose rate of 26 cGy/min with a 10-mV linear accelerator (day -1) (preparation 1). Subsequently, 36 recipients (UPN 315 to 690) received a similar cyclophosphamide preparation, 60 mg/kg/d (days -6 and -5), followed by a midline dose of 1,320 cGy TBI administered in fractions of 165 cGy twice daily for eight doses (days -4, -3, -2, and -1) at a dose rate of 10 cGy/min with a 10-mV linear accelerator (preparation 2). All patients received marrow from allogeneic sibling donors matched at the HLA-A and -B loci and nonreactive in bidirectional mixed lymphocyte culture (day 0).

In 29 cases recipients received acute graft-versus-host disease (GVHD) prophylaxis with methotrexate (MTX) alone at a dose of 15 mg/m² IV on day +1 and 10 mg/m² IV administered at days +3, +6, and...
Table 1. Effect of Selected Features on Outcome of BMT for ANLL

<table>
<thead>
<tr>
<th>Feature</th>
<th>n</th>
<th>Actuarial DFS (95% CI) (%)</th>
<th>P</th>
<th>Actuarial Relapse (95% CI) (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age &lt; 18*</td>
<td>41</td>
<td>61 (45-77)</td>
<td>.89</td>
<td>15 (1-29)</td>
<td>.69</td>
</tr>
<tr>
<td>Recipient age &gt; 18</td>
<td>32</td>
<td>62 (44-80)</td>
<td></td>
<td>9 (0-21)</td>
<td></td>
</tr>
<tr>
<td>Presenting WBC &lt; 20,000/µL*</td>
<td>43</td>
<td>74 (60-88)</td>
<td>.002</td>
<td>7 (0-16)</td>
<td>.02</td>
</tr>
<tr>
<td>Presenting WBC &gt; 20,000/µL</td>
<td>21</td>
<td>26 (3-49)</td>
<td></td>
<td>49 (10-88)</td>
<td></td>
</tr>
<tr>
<td>FAB M4, M5*</td>
<td>12</td>
<td>39 (9-69)</td>
<td>.24</td>
<td>47 (11-83)</td>
<td>.003</td>
</tr>
<tr>
<td>Other FAB</td>
<td>56</td>
<td>66 (53-79)</td>
<td></td>
<td>5 (0-11)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis to CR &lt; 42 d*†</td>
<td>36</td>
<td>57 (40-74)</td>
<td>.54</td>
<td>10 (0-23)</td>
<td>.46</td>
</tr>
<tr>
<td>Diagnosis to CR &gt; 42 d</td>
<td>37</td>
<td>66 (50-82)</td>
<td></td>
<td>16 (1-31)</td>
<td></td>
</tr>
<tr>
<td>CR to BMT &lt; 81 d*</td>
<td>36</td>
<td>57 (40-74)</td>
<td>.50</td>
<td>13 (0-27)</td>
<td>.96</td>
</tr>
<tr>
<td>CR to BMT &gt; 81 d</td>
<td>37</td>
<td>66 (50-82)</td>
<td></td>
<td>13 (0-27)</td>
<td></td>
</tr>
<tr>
<td>Donor/recipient sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/F</td>
<td>17</td>
<td>70 (48-92)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/M</td>
<td>23</td>
<td>45 (23-77)</td>
<td>.20</td>
<td>18 (0-42)</td>
<td>.55</td>
</tr>
<tr>
<td>F/F</td>
<td>17</td>
<td>69 (45-93)</td>
<td></td>
<td>16 (0-38)</td>
<td></td>
</tr>
<tr>
<td>F/M</td>
<td>16</td>
<td>68 (44-92)</td>
<td></td>
<td>16 (0-36)</td>
<td></td>
</tr>
<tr>
<td>Donor/recipient CMV Serology*§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+/−</td>
<td>8</td>
<td>50 (14-86)</td>
<td></td>
<td>20 (0-56)</td>
<td></td>
</tr>
<tr>
<td>+/+</td>
<td>11</td>
<td>44 (14-74)</td>
<td>.40</td>
<td>0</td>
<td>.42</td>
</tr>
<tr>
<td>−/+</td>
<td>15</td>
<td>65 (39-91)</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>−/−</td>
<td>37</td>
<td>66 (50-82)</td>
<td></td>
<td>19 (3-35)</td>
<td>.15</td>
</tr>
<tr>
<td>Single-Dose TBI*</td>
<td>36</td>
<td>56 (40-72)</td>
<td>.30</td>
<td>19 (3-35)</td>
<td></td>
</tr>
<tr>
<td>Fractionated TBI</td>
<td>37</td>
<td>69 (53-82)</td>
<td></td>
<td>5 (0-15)</td>
<td></td>
</tr>
<tr>
<td>MTX GVHD prophylaxis*</td>
<td>29</td>
<td>61 (43-79)</td>
<td>.94</td>
<td>15 (0-31)</td>
<td>.51</td>
</tr>
<tr>
<td>MTX, ATG, Prednisone</td>
<td>41</td>
<td>64 (48-80)</td>
<td></td>
<td>10 (0-23)</td>
<td></td>
</tr>
<tr>
<td>0–1 Acute GVHD]</td>
<td>45</td>
<td>70 (56-74)</td>
<td>.09</td>
<td>10 (0-21)</td>
<td>.49</td>
</tr>
<tr>
<td>II–IV Acute GVHD</td>
<td>28</td>
<td>51 (32-70)</td>
<td></td>
<td>17 (0-34)</td>
<td></td>
</tr>
<tr>
<td>None/limited chronic GVHD]</td>
<td>55</td>
<td>69 (57-81)</td>
<td>.025</td>
<td>10 (0-20)</td>
<td>.44</td>
</tr>
<tr>
<td>Extensive chronic GVHD</td>
<td>18</td>
<td>55 (30-81)</td>
<td></td>
<td>21 (0-48)</td>
<td></td>
</tr>
<tr>
<td>Interstitial pneumonitis]</td>
<td>56</td>
<td>74 (62-86)</td>
<td>.0001</td>
<td>12 (2-22)</td>
<td>.41</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>17</td>
<td>4 (0-9)</td>
<td></td>
<td>25 (0-68)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CMV, cytomegalovirus.

*Pretransplant clinical feature analyzed as univariate.
†Median diagnosis to CR interval, 42 days.
‡Median CR to BMT interval, 81 days.
§CMV complement fixation titer ≥ 1:8 or CMV immunofluorescence titer ≥ 1:40 before BMT.

GVHD

Acute GVHD organ involvement was graded 1 through 4, and chronic GVHD was scored as “limited” or “extensive” by using published criteria.12,13 Grade 1 acute GVHD and limited chronic GVHD were treated with topical steroid cream. Grade 2 through 4 acute GVHD and extensive chronic GVHD were treated with regimens containing systemic steroids and, in some cases, adjunctive therapy with ATG, cyclosporine, or azathioprine.

Data Collection and Statistics

Clinical and laboratory data were retrieved from the University of Minnesota Bone Marrow Transplant Database, which contains systematically and prospectively collected data for all our BMT patients. Univariate analyses were performed by using the Kaplan-Meier product-limit method to assess the effects of various factors on relapse and on DFS (eg, FAB classification, time from diagnosis to BMT, recipient age). The Mantel-Cox test was used to compare the difference in outcomes between groups. The exceptions involved the assessment of the possible influence of GVHD and pneumonitis on outcome. Since GVHD and pneumonitis are not baseline patient characteristics and occur some time after BMT, they were treated as time-dependent covariates in Cox proportional hazards regression analysis. Those factors found to be significantly associated with survival in univariate analyses were then entered into a Cox stepwise multivariate regression analysis to determine their independent contributions to relapse and DFS.
RESULTS

Engraftment

Engraftment was defined as the development of peripheral WBC counts >1,000/µL for three consecutive days following BMT. Sixty-seven of the 73 recipients showed engraftment at a median of 25 days (range, 17 to 43 days). Six patients died at days +9 to +54 of sepsis without peripheral blood evidence of engraftment. There were no late graft failures in nonrelapsing patients.

Relapse

Six of 67 recipients showing engraftment relapsed at +3 to +25 months. The Kaplan-Meier estimate of the relapse rate is 13% (95% CI, 3% to 23%) at 4 years. Characteristics of relapsing patients are shown in Table 2.

Survival and Cause of Death

Twenty-six of 73 patients died from 9 to 1,311 days (43 months) following BMT. The Kaplan-Meier estimate of survival is 60% (95% CI, 48% to 72%) at 4 years. Principal causes of death are listed in Table 3. Thirty-six of 47 survivors have Karnofsky activity assessments of 100%. Reasons for impaired activity assessment in 11 surviving recipients are listed in Table 4.

Association of Patient Characteristics and Transplant Events With Outcome

Age. The actuarial DFS rate is 61% (95% CI, 45% to 77%) in children and 62% (95% CI, 44% to 80%) in adults at 7 years (P = .89) (Fig 1). The 57% (95% CI, 31% to 83%) long-term projected DFS rate seen in 14 recipients between 31 and 45 years did not differ significantly from that seen in recipients of transplants in earlier decades of life (P = .59, Table 5). The actuarial relapse rate is 15% (95% CI, 1% to 29%) in children and 9% (95% CI, 0% to 21%) in adults (P = .69, Fig 1). No significant association of age with outcome could be identified in univariate analysis (Table 1); moreover, after adjustment for features found to be significant in multivariate analysis, age >18 years had no significant impact on either DFS (P = .29, Table 6) or on relapse (P = .86, Table 7).

Presenting WBC count. Presenting WBC counts could be verified in 64 cases. Forty-three patients presented with peripheral WBC counts <20,000/µL (median, 4,000/µL; range, 800 to 18,600/µL). Twenty-one patients presented with peripheral WBC counts >20,000/µL (median, 59,600/µL; range, 21,000 to 228,000/µL; Table 1). Initial presentation with a peripheral blood WBC count >20,000/µL independently predicted poor DFS when entered into stepwise regression analyses including not only prognostic features but also posttransplant events with potential bearing on outcome (P = .01, Table 6).

Table 2. Characteristics of Relapsed Patients

<table>
<thead>
<tr>
<th>UPN</th>
<th>Recipient Age (yr)</th>
<th>Preparation*</th>
<th>FAB</th>
<th>Presenting WBC Count (/µL)</th>
<th>Days to Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>11.1</td>
<td>1</td>
<td>M4</td>
<td>24,300</td>
<td>735</td>
</tr>
<tr>
<td>106</td>
<td>13.3</td>
<td>1</td>
<td>M4</td>
<td>149,000</td>
<td>756</td>
</tr>
<tr>
<td>118</td>
<td>6.5</td>
<td>1</td>
<td>M2</td>
<td>40,600</td>
<td>195</td>
</tr>
<tr>
<td>201</td>
<td>28.8</td>
<td>1</td>
<td>M2</td>
<td>120,000</td>
<td>92</td>
</tr>
<tr>
<td>208</td>
<td>16.5</td>
<td>1</td>
<td>M5</td>
<td>5,200</td>
<td>323</td>
</tr>
<tr>
<td>592</td>
<td>24.7</td>
<td>2</td>
<td>M4</td>
<td>5,900</td>
<td>456</td>
</tr>
</tbody>
</table>

*Preparation 1 contains 750 cGy single-dose irradiation. Preparation 2 contains a total of 1,320 cGy fractionated irradiation administered twice daily to eight doses. Refer to Methods for details.

Table 3. Principal Causes of Death

<table>
<thead>
<tr>
<th>Cause*</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>5</td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>Aspergillus sp</td>
<td>3</td>
</tr>
<tr>
<td>Candida sp</td>
<td>2</td>
</tr>
<tr>
<td>Staphylococcus sp</td>
<td>2</td>
</tr>
<tr>
<td>Enterococcus sp</td>
<td>1</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1</td>
</tr>
<tr>
<td>CMV</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>4</td>
</tr>
<tr>
<td>RSV</td>
<td>1</td>
</tr>
<tr>
<td>Candida sp</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas sp</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>2</td>
</tr>
<tr>
<td>B-cell lymphoproliferation</td>
<td>1</td>
</tr>
<tr>
<td>Liver failure</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
</tr>
</tbody>
</table>

Abbreviation: RSV, respiratory syncitial virus.

*GVHD has been excluded as a principal cause of death but was implicated in nine of 26 deaths.

with peripheral WBC counts >20,000/µL (median, 59,600/µL; range, 21,000 to 228,000/µL; Table 1). Initial presentation with a peripheral blood WBC count >20,000/µL independently predicted poor DFS when entered into stepwise regression analyses including not only prognostic features but also posttransplant events with potential bearing on outcome (P = .01, Table 6). Although presentation with an

Table 4. Cause of Impaired Activity Assessments in BMT Recipients

<table>
<thead>
<tr>
<th>UPN</th>
<th>Karnofsky (%)</th>
<th>Impairment</th>
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</thead>
<tbody>
<tr>
<td>354</td>
<td>70</td>
<td>Avascular necrosis, hip*</td>
</tr>
<tr>
<td>523</td>
<td>70</td>
<td>Blindness*</td>
</tr>
<tr>
<td>315</td>
<td>90</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>405</td>
<td>90</td>
<td>Obstructive lung disease*</td>
</tr>
<tr>
<td>499</td>
<td>90</td>
<td>Obstructive lung disease</td>
</tr>
<tr>
<td>510</td>
<td>90</td>
<td>Chronic interstitial nephritis</td>
</tr>
<tr>
<td>522</td>
<td>90</td>
<td>Avascular necrosis, hip</td>
</tr>
<tr>
<td>592</td>
<td>90</td>
<td>Obstructive lung disease</td>
</tr>
<tr>
<td>678</td>
<td>90</td>
<td>UGI GVHD*</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; UGI, upper gastrointestinal.

*Impairment attributed to GVHD or GVHD therapy.
increased WBC count was significantly associated with relapse in univariate analysis \((P = .02)\), an independent association with relapse could not be demonstrated in multivariate analysis \((P = .10, \text{Table 7})\).

**FAB subtype.** Assignment of presenting FAB subtype was made after a review of original bone marrow and peripheral blood smears at our institution by a qualified observer (R.B.) who was unaware of patient outcome. In the five cases where presenting material was unavailable for review, patients were excluded from analysis. While initial presentation with a monocytic subtype of ANLL (FAB M4, M5) seen in 12 recipients did not significantly affect DFS when compared with those not presenting with a monocytic subtype, it correlated significantly with relapse in univariate analysis \((P = .003, \text{Fig 2})\) and when entered into stepwise multivariate analysis \((P = .01, \text{Table 7})\).

**TBI preparation.** Although improved DFS \((P = .30)\) and relapse rates \((P = .15)\) could be seen in recipients of fractionated TBI when compared with single-dose TBI in univariate analysis (Table 1), no independent effect of TBI preparation on DFS or on relapse rate \((P = .27, \text{Table 7})\) could be demonstrated in multivariate analysis.

**Other potential prognostic features.** As demonstrated in Table 1, no significant association between interval from diagnosis to CR, interval from CR to BMT, donor/recipient sex combinations, pre-BMT donor/recipient CMV serologies, or acute GVHD prophylaxis regimens and outcome could be demonstrated. An unexplained trend toward poorer DFS \((P = .07)\) could be discerned, however, in male recipients of male donor marrow (Table 6).

**GVHD.** The actuarial incidence of grades 2 through 4 acute GVHD was 40% \((95\% \text{ CI}, 28\% \text{ to } 52\%)\) at 3 months. The occurrence of grades 2 through 4 acute GVHD was more common in recipients >18 years of age \((P = .03)\). The development of grades 2 through 4 acute GVHD independently predicted poor DFS in multivariate analysis \((P = .03, \text{Table 6})\); however, no such independent effect on relapse could be identified.

Twenty-three of 59 evaluable patients developed chronic GVHD. Although the development of extensive chronic GVHD could be correlated with decreased DFS in univariate analysis \((P = .025)\), an independent correlation with neither DFS \((P = .85, \text{Table 6})\) nor relapse could be identified in multivariate analysis.

**Interstitial pneumonitis.** Seventeen patients developed viral or idiopathic interstitial pneumonitis. Among seven cases of interstitial pneumonitis in which a viral etiology could be identified (5 CMV, 1 RSV, 1 herpes simplex virus [HSV]), four cases of CMV and one case of RSV were fatal. Two of ten cases of idiopathic interstitial pneumonitis were fatal. The 25% incidence \((95\% \text{ CI}, 9\% \text{ to } 41\%)\) of viral and idiopathic interstitial pneumonitis seen in 36 recipients of single-dose TBI did not differ significantly from the 29% incidence \((95\% \text{ CI}, 13\% \text{ to } 43\%)\) seen in 37 recipients of fractionated TBI \((P = .82)\). The cases of idiopathic interstitial pneumonitis were evenly divided between the two treatment groups. No effect of recipient age on the development of interstitial pneumonitis could be discerned in univariate analysis \((P = .45)\). The development of interstitial pneumonitis was highly correlated with poor DFS in multivariate analysis \((P = .001, \text{Table 6})\).

**DISCUSSION.**

We demonstrate that BMT with major histocompatibility complex-matched sibling marrow provides a low relapse rate and excellent DFS for transplant recipients in first CR from ANLL. A comparison of recipients <18 years old (median, 13.6 years) with those >18 years old (median, 28.6 years) shows virtually identical survival, DFS, and relapse rates.

### Table 6. Effect of Patient Characteristics on DFS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(P) Value</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial pneumonitis</td>
<td>.00</td>
<td>9.1</td>
</tr>
<tr>
<td>Presenting WBC count &gt;20,000/μL</td>
<td>.01</td>
<td>3.8</td>
</tr>
<tr>
<td>Acute GVHD 2 through 4</td>
<td>.03</td>
<td>2.9</td>
</tr>
<tr>
<td>M recipient and M donor</td>
<td>.07</td>
<td>2.2</td>
</tr>
<tr>
<td>Age &gt;18 yr</td>
<td>.29</td>
<td>—</td>
</tr>
</tbody>
</table>

### Table 7. Effect of Patient Characteristics on Relapse

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(P) Value</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAB M4, M5</td>
<td>.01</td>
<td>8.7</td>
</tr>
<tr>
<td>Presenting WBC count &gt;20,000/μL</td>
<td>.10</td>
<td>—</td>
</tr>
<tr>
<td>Preparative regimen</td>
<td>.27</td>
<td>—</td>
</tr>
<tr>
<td>Age &gt;18 yr</td>
<td>.66</td>
<td>—</td>
</tr>
</tbody>
</table>
older recipients, however, agrees with an earlier report of the
earlier in life (Table 5). These findings differ from those of
significantly from that of patients who received transplants
The 57% Kaplan-Meier estimate of DFS seen in 15 recip-
subtypes.
M4 or M5 subtype. Solid lines represent results in 56
patients receiving allogeneic BMT as therapy for first CR ANLL.
was reported after BMT therapy for first CR from ANLL.8
Moreover, an increased relapse rate in patients presenting
ANLL in childre&9 and in two recent studies of BMT
actively correlated with decreased DFS in this study, and
ANLL8 and that of others who have seen a protective effect of acute or chronic
GVHD after BMT for first-remission ANLL9 and from that
other patient characteristic could be shown to have an
independent effect on outcome. Preparation with either the
single-dose or the fractionated TBI regimens described here
was associated with an equivalent incidence of idiopathic
GVHD or its therapy.
FAB M1M23M6M7
1.0
.8
.6
.4
.2
0
0 1 2 3 4 5 6 7 8 9 10
Fig 2. Kaplan-Meier product-limit estimates of relapse in 68
patients receiving allogeneic BMT as therapy for first CR ANLL.
Dashed lines represent results in 12 patients presenting originally
with FAB M4 or M5 subtype. Solid lines represent results in 56
patients presenting originally with M1, M2, M3, M6, or M7
subtypes.
The 57% Kaplan-Meier estimate of DFS seen in 15 recip-
ients between the ages of 31 and 45 years does not differ
significantly from that of patients who received transplants
earlier in life (Table 5). These findings differ from those of
Clift et al who reported a significant trend of decreasing DFS
with increasing age in univariate analysis, although the rate
of decrease with advancing age was slightly above the age of
20 years.9 The finding of equivalent survival in younger and
older recipients, however, agrees with an earlier report of the
International Bone Marrow Transplant Registry15 and with a
more recent report in which no significant adverse effect of
recipient age (range, 1 to 41 years) on DFS posttransplant
for first CR from ANLL could be demonstrated.9
In this study several presenting patient characteristics
affected the outcome of BMT. The 47% estimated relapse
rate seen in recipients presenting with morphologic evidence
of a monocytic component (FAB M4, M5) was significantly
higher than the 5% estimated relapse rate seen in patients
presenting with other FAB subtypes (Fig 2 and Table 7).
Although an increased relapse rate in patients presenting
with FAB M4 or M5 morphology has been reported after
conventional therapy16-18 and after BMT,67 no such correla-
tion could be found in a recent report of BMT for first CR
from ANLL in children19 and in two recent studies of BMT
therapy of ANLL in young adults.68 The finding of a higher
post-BMT relapse rate in patients presenting with a mono-
cytic subtype of ANLL suggests that preparation for BMT
with additional agents known to have antitumor activity may
be useful in this situation.20
The 26% estimated DFS seen in recipients presenting with
a peripheral WBC count >20,000/μL is significantly worse
than the 74% DFS seen in patients presenting with lower
peripheral WBC counts (Table 1). This significant decrease
in DFS persisted in multivariate analysis (Table 7). Although
the association of elevated peripheral WBC counts and
decreased DFS cannot be attributed to relapse in this
study, a trend toward relapse in patients presenting with an
elevated WBC count is seen (Table 7), and the possibility
exists that analysis after prolonged follow-up or additional
patient accrual may demonstrate such an association. The
finding of a correlation between a high presenting peripheral
WBC count and poorer DFS supports our earlier observation
of this effect in BMT recipients.7 Similarly, an adverse effect
of elevated peripheral WBC count on the outcome of conven-
tional therapy for ANLL has been reported.21 This finding,
however, differs from that of Clift et al who could not
demonstrate a correlation between presenting WBC count
and DFS.9 Similarly, Forman et al found no relationship
between presenting peripheral WBC count and outcome
after BMT therapy for first CR from ANLL.8
In addition to pretransplant patient characteristics several
posttransplant events could be independently associated with
Poor outcome. The development of interstitial pneumonitis
was highly correlated with decreased DFS in this study, and
has been associated with poor outcome in other reports.22,23
The development of grades 2 through 4 acute GVHD was
also independently associated with poor DFS (Table 6). In
this study, the development of extensive chronic GVHD did
not independently affect DFS, and the development of
neither acute nor chronic GVHD could be independently
associated with protection from relapse. This result differs
from that of Clift et al who reported significantly decreased
relapse rates in recipients who developed extensive chronic
GVHD after BMT for first-remission ANLL9 and from that
of others who have seen a protective effect of acute or chronic
GVHD against relapse in patients receiving BMT as therapy
for ANLL24 and other leukemias.25
No other patient characteristic could be shown to have an
independent effect on outcome. Preparation with either the
single-dose or the fractionated TBI regimens described here
was associated with an equivalent incidence of idiopathic
interstitial pneumonitis and had no significant bearing on
DFS or rate of relapse in multivariate analysis. It should be
noted, however, that five of six relapses occurred in recipients
of single-dose irradiation. A comparison of the two prepara-
tive regimens reported here should be viewed with care since
the regimens were used consecutively and no attempt was
made to standardize dose rate, total TBI dose, or antileu-
kemic effect.
A single, principal cause of death is often difficult to
assign when evaluating the consequences of BMT therapy. In
this series systemic infection was an important factor in the
death of 17 recipients, while pneumonia and GVHD could be
implicated in the death of nine recipients each (Table 3).
An analysis of BMT therapy that uses DFS and relapse as
the exclusive measures of outcome by no means reflects the
impact of the procedure on BMT recipients. Eleven of 47
survivors experience some degree of debility as a direct
consequence of BMT therapy, and in at least three cases this
debility has resulted in marked impairment of activity (Table
4). In six of the cases activity impairment is a direct
consequence of GVHD or its therapy.
This study suggests that allogeneic BMT can provide
sustained DFS in the majority of patients undergoing ther-
apy during first CR of ANLL. Young adults 18 to 45 years
of age have an outcome that compares favorably with that of
children who receive transplants under identical conditions,
and BMT therapy should not be withheld from this patient
group. Presentation with FAB M4 or M5 subtype independently predicts an increased risk of relapse, which suggests that a more aggressive approach to leukemia ablation is warranted in these recipients. Larger, multicenter, prospective trials using standardized reference laboratories, preparative regimens, GVHD prophylaxis and therapy, and support protocols may be necessary to resolve apparent discrepancies in the relative importance of various patient characteristics on the outcome of BMT that are reported in current studies.

REFERENCES


Allogeneic bone marrow transplantation for acute nonlymphocytic leukemia in first remission

PB McGlave, RJ Haake, BC Bostrom, R Brunning, DD Hurd, TH Kim, ME Nesbit, GM Vercellotti, D Weisdorf and WG Woods