Data for 595 patients with severe aplastic anemia receiving HLA-identical sibling bone marrow transplants were analyzed to determine the effect of pretransplant conditioning and graft-versus-host disease (GVHD) prophylaxis on outcome. Transplants were performed between 1980 and 1987 and reported to the International Bone Marrow Transplant Registry. Three conditioning regimens (cyclophosphamide alone, cyclophosphamide plus limited field irradiation, and cyclophosphamide plus total body irradiation) were studied; none was associated with superior long-term survival. Three GVHD prophylaxis regimens (methotrexate, cyclosporine, and methotrexate plus cyclosporine) were studied. Recipients of cyclosporine with or without methotrexate had a significantly higher probability of 5-year survival (89%, 95% confidence interval 63% to 74%) than patients receiving methotrexate only (56%, 49% to 62%, \( P < .003 \)). Higher survival with cyclosporine resulted from decreased risks of interstitial pneumonia (\( P < .0002 \)) and chronic GVHD (\( P < .005 \)). Additional risk factors adversely associated with survival included infection pretransplant (\( P < .004 \)), use of parous or transfused female donors (\( P < .005 \)), older patient age (\( P < .005 \)), and 20 or more pretransplant transfusions (\( P < .008 \)). These data may prove useful in planning randomized clinical trials and in identifying patients at high-risk of treatment failure.

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MATERIALS AND METHODS

Patients and treatment. Six hundred thirty-seven patients receiving HLA-identical sibling transplants for acquired severe aplastic anemia were reported to the International Bone Marrow Transplant Registry between 1980 and 1987. From the International Bone Marrow Transplant Registry and the Aplastic Anemia Working Party of the European Bone Marrow Transplant Group; and Service d’Hematologie, Hôpital St Louis, Paris, France; Divisions of Cancer and Blood Diseases and Biostatistics/Clinical Epidemiology, and the Departments of Pediatrics and Medicine, Medical College of Wisconsin, Milwaukee; the Department of Hematology, M.D. Anderson Cancer Center, Houston, TX; the Department of Hematology, Hammersmith Hospital, London, UK; the Division di Ematologia, Ospedale San Martino, Genoa, Italy; the Department of Hematology, St Vincent’s Hospital, Sydney, Australia; the Department of Hematology/Oncology, UCLA Center for the Health Sciences, Los Angeles, CA; the Department of Haematology, St George’s Hospital Medical School, London, UK; the Department of Hematology, Center for Adult Diseases, Osaka, Japan; the Department of Pediatrics, University of Minnesota, Minneapolis; the Department of Hematology, University of Barcelona, Spain; and the Department of Hematology, University of Basel, Switzerland.


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Bone marrow transplantation from an HLA-identical sibling is effective therapy for severe aplastic anemia resulting in 60% to 80% long-term, disease-free survival.1-3 Results of transplants for aplastic anemia improved over the past decade.4-9 Factors frequently reported to predict good outcome include younger recipient age, absence of pretransplant infections, no or few pretransplant transfusions, and use of female donors.10 Other factors sometimes reported to affect survival include pretransplant response to platelet transfusions and bone marrow dose.4,11,12

Patients typically receive pretransplant conditioning designed to prevent graft rejection and posttransplant immune suppression designed to prevent or modify graft-versus-host disease (GVHD). There is no large study comparing the efficacy of various pretransplant and posttransplant regimens. Initially, most transplant regimens for aplastic anemia used cyclophosphamide 200 mg/kg pretransplant and methotrexate posttransplant.13 Graft failure occurred in 30% to 50% of patients; disease-free survival was about 40%. Modifications, designed primarily to reduce graft failure, were subsequently introduced.5,8,12 These most commonly involved adding total body radiation (TBR) or limited field irradiation (LFR, total lymphoid or thoracoabdominal radiation) to cyclophosphamide for conditioning.5,8,12 Another approach was to infuse donor buffy coat cells posttransplant to improve engraftment.5,10

Changes in posttransplant immune suppression were also made. Cyclosporine was introduced for GVHD prophylaxis in the 1980s.5 Some studies reported more rapid engraftment and less interstitial pneumonia with cyclosporine, although it appeared comparable with methotrexate in preventing GVHD.17-20 Recent reports suggest that combined cyclosporine and methotrexate reduces the incidence and severity of acute GVHD as compared with either agent alone.5,8,12,21

The major limitation of studies of transplant regimens in aplastic anemia is small numbers of patients, usually less than 100. The purpose of this study was to evaluate the impact of different pretransplant conditioning and GVHD prophylaxis regimens (referred to as treatment regimens) on outcome of 595 HLA-identical sibling bone marrow transplants for severe aplastic anemia.

Bone Marrow Transplantation for Severe Aplastic Anemia: Influence of Conditioning and Graft-Versus-Host Disease Prophylaxis Regimens on Outcome

Table 1. Treatment Regimens Used for Bone Marrow Transplantation in Severe Aplastic Anemia

<table>
<thead>
<tr>
<th>Preparative</th>
<th>GVHD Prophylaxis</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>CY (200 mg/kg, n = 292; 120 mg/kg, n = 9)</td>
<td>MTX 116</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CsA 142</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MTX + CsA 43</td>
<td></td>
</tr>
<tr>
<td>CY (200 mg/kg, n = 132; 120 mg/kg, n = 80) + LFR (median 6 Gy, range 1.5-15 Gy)</td>
<td>MTX 78</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CsA 102</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CsA + MTX 32</td>
<td></td>
</tr>
<tr>
<td>CY (200 mg/kg, n = 70; 120 mg/kg, n = 12) + TBR (median 3 Gy, range 3-11.25 Gy)</td>
<td>MTX 60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CsA 22</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CY, cyclophosphamide; MTX, methotrexate; CsA, cyclosporine; LFR, limited field radiation including total lymphoid radiation and thoracoabdominal radiation; TBR, total body radiation.

plant Registry (IBMTR) between 1980 and 1987; transplants for hereditary forms of aplastic anemia or cytopenia associated with myelodysplasia were not considered. All patients fulfilled published hematologic criteria for severe aplastic anemia. Pretransplant cytogenetic data were not reported. This study was restricted to 595 patients receiving the eight most commonly used treatment regimens (Table 1). The remaining 42 patients received a variety of regimens with too few patients in any one group for separate analysis. Patient and treatment characteristics are shown in Table 2.

Twenty-six patients received second transplants; these patients were described previously. Outcome variables. Graft failure was analyzed in patients surviving ≥21 days posttransplant using published criteria; both primary nonengraftment and transient engraftment were included. Grade II-IV acute GVHD was defined using published criteria; patients surviving ≥21 days with engraftment were considered at risk. Chronic GVHD was defined by clinical criteria in subjects surviving ≥90 days with engraftment. Interstitial pneumonia was defined as nonbacterial pneumonia, characterized by bilateral diffuse interstitial infiltrates; it was categorized as early (occurring <4 months posttransplant) or late (occurring 4 or more months posttransplant). In 84% of cases the diagnosis was proved by bronchoalveolar lavage, biopsy or autopsy; 16% of cases were diagnosed solely by clinical criteria.

Statistical methods. Patient-, donor-, and disease-related variables in Table 3 were compared among the eight treatment groups using analysis of variance. Groups differed in proportion of persons receiving antithymocyte globulin pretransplant, numbers of pretransplant transfusions, pretransplant performance scores, bone marrow cell dose, type of isolation, granulocyte levels pretransplant, use of donor buffy-coat cell transfusions, and interval between diagnosis and transplant. Cox proportional hazards regression models with age and year of transplant as covariates were used to evaluate the impact of treatment regimen on outcome and to calculate adjusted probabilities of transplant outcomes.

To identify variables, treatment-related or not, independently predicting survival, a stepwise backward elimination procedure was used. Briefly, variables to be considered were entered in an initial regression model, with time to death as the outcome. Statistically insignificant (P > .05) factors were removed from the model one at a time with re-estimation of model variables after each step. Variable elimination was stopped when all remaining factors were significant at P < .05.

Results of regression analyses were examined for potentially confounding differences among centers by: (1) entering center size (defined as number of transplants performed annually during the study period) as a covariate in the regression equations; (2) stratifying by center size (< and >10 transplants a year); and (3) repeating the analysis after randomly excluding centers (bootstrap). Results were not affected by these adjustments; the effect of

Table 2. Patient, Disease, and Treatment Characteristics of 595 Recipients of HLA-Identical Sibling Transplants for Severe Aplastic Anemia

<table>
<thead>
<tr>
<th>Etiology of aplasia</th>
<th>Evaluable</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>466/595</td>
<td>78</td>
</tr>
<tr>
<td>Drug-related</td>
<td>54/595</td>
<td>9</td>
</tr>
<tr>
<td>Hepatitis-related</td>
<td>57/595</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>18/595</td>
<td>3</td>
</tr>
</tbody>
</table>

Year of transplant

1981-82 | 129/595 | 21 |
1983-84 | 171/595 | 28 |
1985-86 | 155/595 | 26 |
1987 | 141/595 | 24 |

Patient characteristics

Age (yr)

0-10 | 98/595 | 17 |
11-20 | 227/595 | 38 |
21-30 | 186/595 | 31 |
31-40 | 60/595 | 10 |
>40 | 24/595 | 4 |

Clinically significant organ impairment pretransplant

68/592 | 11 |

Clinically important infection in week before transplant

213/595 | 36 |

Performance score < 90%

221/595 | 37 |

Donor characteristics

Age (yr)

0-10 | 103/589 | 17 |
11-20 | 204/589 | 35 |
21-30 | 169/589 | 29 |
31-40 | 89/589 | 15 |
>40 | 24/589 | 4 |

Female alloimmunized by pregnancy or transfusion

62/229 | 27 |

Donor-recipient matched for ABO type

382/578 | 66 |

Donor-recipient sex-match

Male → male | 198/595 | 33 |
Male → female | 111/595 | 19 |
Female → female | 118/595 | 20 |
Female → male | 168/595 | 28 |

Pretransplant therapy

Laminar air flow isolation

206/595 | 45 |

No. of transfusions

None | 23/595 | 4 |
1-19 | 251/595 | 42 |
≥20 | 321/595 | 54 |

Interval between diagnosis and transplant

<1 mo | 120/588 | 20 |
1-2 mo | 165/588 | 28 |
>2 mo | 303/588 | 52 |

Treatment for aplasia pretransplant

None | 251/595 | 42 |
Corticosteroids only | 121/595 | 20 |
Androgens + corticosteroids ± other | 144/595 | 24 |
Androgens only | 71/595 | 12 |
Other | 8/595 | 1 |

Posttransplant therapy

Buffy coat cells administered | 165/595 | 28 |
treatment regimen and other variables appeared to be similar at small and large centers.

All $P$ values are two-sided and derived from multivariate analyses unless otherwise specified. Because of the multiple comparisons made, we considered only $P$ values $< .01$ statistically significant.\textsuperscript{19} $P$ values $> .01$ and $< .05$ are considered marginal and presented to show trends; they should be interpreted cautiously.

**RESULTS**

The incidence of graft failure among 567 patients at risk was 10%. Moderate to severe acute GVHD occurred in 221 of 558 (40%) patients at risk. Chronic GVHD developed in 212 of 469 (45%) patients at risk. There were 81 cases of interstitial pneumonia; 66 cases occurred early and 15 late. Interstitial pneumonia was due to cytomegalovirus in 30 cases, other viruses in 6 cases, *Pneumocystis carinii* in 4, and fungal infection in 10; 31 cases were idiopathic. The actuarial probability (95% confidence interval) of interstitial pneumonia at 3 years was 15% (12% to 19%). The 5-year actuarial probability of survival for the 595 patients was 63% (58% to 67%).

**Treatment regimen.** Two-year probabilities of outcomes for the eight treatment groups, adjusted for patient and disease variables, are shown in Table 4.

Although the 43 patients receiving cyclophosphamide alone for conditioning and combined methotrexate + cyclosporine for GVHD prophylaxis (group 7) had the highest probability of survival (80% [65% to 90%]), this was not significantly different from those receiving cyclophosphamide + TBR + cyclosporine (group 6; 76% [56% to 89%]), cyclophosphamide + cyclosporine (group 4; 72% [64% to 79%]), cyclophosphamide + LFR + cyclosporine (group 5; 67% [58% to 75%]), or cyclophosphamide + LFR + methotrexate + cyclosporine (group 8; 63% [45% to 78%]). The probability of survival with cyclophosphamide + cyclosporine + methotrexate (group 7) was marginally higher than with cyclophosphamide + methotrexate (group 1; 63% [53% to 72%], $P < .03$) and cyclophosphamide + LFR + methotrexate (group 2; 59% [48% to 69%], $P < .02$) and significantly higher than with cyclophosphamide +

| P value\textsuperscript{†} | < .004 | < .02 | < .02 | < .0009 | < .05 |
---|---|---|---|---|---|

**Table 3. Patient, Donor, and Transplant Variables Examined for Comparability Among the Eight Treatment Regimens**

<table>
<thead>
<tr>
<th>Variable</th>
<th>CY + MTX</th>
<th>CY + LFR + MTX</th>
<th>CY + TBR + MTX</th>
<th>CY + CsA</th>
<th>CY + LFR + CsA</th>
<th>CY + TBR + CsA</th>
<th>CY + CsA + MTX</th>
<th>CY + LFR + MTX + CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretransplant performance score*</td>
<td>3 (1-17)</td>
<td>4 (1-4)</td>
<td>6 (2-39)</td>
<td>3 (1.90)</td>
<td>5 (17-69)</td>
<td>8 (4-85)</td>
<td>3 (1-2)</td>
<td>4 (1-2)</td>
</tr>
<tr>
<td>No. of pretransplant transfusions*</td>
<td>19 (8-32)</td>
<td>42 (31-63)</td>
<td>47 (34-60)</td>
<td>32 (31-53)</td>
<td>47 (28-74)</td>
<td>43 (20-58)</td>
<td>43 (28-47)</td>
<td>47 (28-47)</td>
</tr>
<tr>
<td>Marrow cell dose*</td>
<td>32 (12-28)</td>
<td>61 (42-66)</td>
<td>43 (29-58)</td>
<td>32 (24-41)</td>
<td>43 (28-47)</td>
<td>37 (5-16)</td>
<td>51 (40-62)</td>
<td>51 (40-62)</td>
</tr>
<tr>
<td>Donor age</td>
<td>78 (43-116)</td>
<td>97 (48-146)</td>
<td>221 (104-378)</td>
<td>121 (69-253)</td>
<td>220 (110-398)</td>
<td>211 (110-377)</td>
<td>210 (110-377)</td>
<td>210 (110-377)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of pretransplant transfusions*</th>
<th>CY + MTX</th>
<th>CY + LFR + MTX</th>
<th>CY + TBR + MTX</th>
<th>CY + CsA</th>
<th>CY + LFR + CsA</th>
<th>CY + TBR + CsA</th>
<th>CY + CsA + MTX</th>
<th>CY + LFR + MTX + CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretransplant performance score*</td>
<td>3 (1-17)</td>
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<td>6 (2-39)</td>
<td>3 (1.90)</td>
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<td>8 (4-85)</td>
<td>3 (1-2)</td>
<td>4 (1-2)</td>
</tr>
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<td>19 (8-32)</td>
<td>42 (31-63)</td>
<td>47 (34-60)</td>
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<td>47 (28-74)</td>
<td>43 (20-58)</td>
<td>43 (28-47)</td>
<td>47 (28-47)</td>
</tr>
<tr>
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<td>32 (12-28)</td>
<td>61 (42-66)</td>
<td>43 (29-58)</td>
<td>32 (24-41)</td>
<td>43 (28-47)</td>
<td>37 (5-16)</td>
<td>51 (40-62)</td>
<td>51 (40-62)</td>
</tr>
<tr>
<td>Donor age</td>
<td>78 (43-116)</td>
<td>97 (48-146)</td>
<td>221 (104-378)</td>
<td>121 (69-253)</td>
<td>220 (110-398)</td>
<td>211 (110-377)</td>
<td>210 (110-377)</td>
<td>210 (110-377)</td>
</tr>
</tbody>
</table>

**Table 4. Results of Multivariate Analyses Comparing Outcome of Patients Transplanted for Severe Aplastic Anemia According to Treatment Regimen Used**

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment Regimen</th>
<th>N</th>
<th>Graft Failure</th>
<th>Acute GVHD</th>
<th>Chronic GVHD</th>
<th>Interstitial Pneumonia</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CY + MTX</td>
<td>116</td>
<td>19</td>
<td>32</td>
<td>54</td>
<td>18</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>CY + LFR + MTX</td>
<td>78</td>
<td>8</td>
<td>42</td>
<td>61</td>
<td>21</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>CY + TBR + MTX</td>
<td>60</td>
<td>3</td>
<td>47</td>
<td>43</td>
<td>31</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>CY + CsA</td>
<td>142</td>
<td>9</td>
<td>32</td>
<td>37</td>
<td>9</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>CY + LFR + CsA</td>
<td>102</td>
<td>3</td>
<td>53</td>
<td>51</td>
<td>7</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>CY + TBR + CsA</td>
<td>22</td>
<td>3</td>
<td>39</td>
<td>33</td>
<td>5</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>CY + CsA + MTX</td>
<td>43</td>
<td>9</td>
<td>21</td>
<td>26</td>
<td>9</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>CY + LFR + MTX + CsA</td>
<td>32</td>
<td>10</td>
<td>35</td>
<td>43</td>
<td>24</td>
<td>63</td>
</tr>
</tbody>
</table>

Abbreviations: CY, cyclophosphamide; MTX, methotrexate; CsA, cyclosporine.

\*Adjusted for differences in age, pretransplant performance score, previous treatment with antithymocyte globulin, number of pretransplant transfusions, type of isolation used, marrow cell dose administered, pretransplant granulocyte count, donoruffy coat cells given posttransplant, interval between diagnosis and transplant and year of transplant.

\†Derived from multivariate Cox regression model with treatment regimen entered as a categorical variable.
TBR + methotrexate (group 3; 55% [43% to 67%], \( P < .009 \)).

**Conditioning regimens.** After determining that treatment regimen was significantly associated with outcome, we next studied whether pretransplant conditioning or post-transplant immune suppression was more important by examining each separately. Conditioning regimens were considered in three categories: (1) cyclophosphamide alone (groups 1, 4, and 7 in Table 4); (2) cyclophosphamide + LFR (groups 2, 5, and 8); and (3) cyclophosphamide + TBR (groups 3 and 6). Use of LFR or TBR was significantly associated with decreased graft failure compared with cyclophosphamide alone; LFR was significantly and TBR marginally associated with increased acute GVHD in Cox regression models adjusted for GVHD prophylaxis and patient and disease variables (Fig 1). LFR was marginally associated with increased chronic GVHD compared with cyclophosphamide alone. Both forms of radiation were associated with increases in the risk of interstitial pneumonia that were not statistically significant. When early and late cases were considered separately, TBR (relative risk 2.2, \( P < .05 \)) but not LFR (relative risk 1.2, \( P = \text{not significant} \)) was marginally associated with an increased risk of early interstitial pneumonia compared with cyclophosphamide alone. There was no association between radiation and late interstitial pneumonia. There were no significant differences in posttransplant mortality among the three conditioning regimens. This was true for those at high risk of graft failure, ie, multiply transfused. Radiation dose and schedule and cyclophosphamide dose, within the ranges studied (Table 1), were not significantly associated with outcome in these models.

**GVHD prophylaxis.** Three regimens were studied: (1) methotrexate, (2) cyclosporine, and (3) combined methotrexate + cyclosporine. Cyclosporine alone was marginally associated with lower risk of graft failure (\( P < .02 \)) and significantly associated with lower risk of interstitial pneumonia (both early and late) than methotrexate alone (\( P < .002 \)) after adjusting for conditioning regimen and patient and disease characteristics (Fig 2). The risks of graft failure and interstitial pneumonia with combined methotrexate + cyclosporine were intermediate and not significantly different from either drug alone. The risk of chronic GVHD was similar with combined methotrexate + cyclosporine and cyclosporine alone; the risk with methotrexate alone was higher than with either of the other regimens, although the difference from combined methotrexate + cyclosporine was only marginally significant (Fig 2). Patients receiving cyclosporine alone or combined with methotrexate had lower mortality than those receiving methotrexate alone (Fig 2). Mortality with combined methotrexate + cyclosporine was similar to mortality with cyclosporine alone. The 5-year probability of survival was 69% (63% to 74%) with cyclosporine (with or without methotrexate) and 56% (49% to 62%) with methotrexate without cyclosporine (\( P < .003 \), Fig 3).

**Other variables associated with survival.** The variables in Table 3 were examined for their association with survival after bone marrow transplant using a Cox regression model that included treatment regimen as a covariate (Table 5). Risk of treatment failure (death from any cause) increased with clinically important infection in the week before transplant (\( P < .004 \)), increasing age (\( P < .005 \)), use of parous or transfused female donors (\( P < .005 \)), more than 20 transfusions pretransplant (\( P < .006 \)), and interval between diagnosis and transplant more than 1 month (\( P < .02 \)). Pretransplant therapy for aplastic anemia, bone marrow cell dose, and donor buffy coat infusions were not significantly associated with treatment failure.
Causes of treatment failure differed with different preparative regimens. There was less graft failure and more GVHD with regimens including radiation. A similar pattern of less graft failure and more chronic GVHD is reported with transfusion of donor leukocytes posttransplant.14 This may result from similar effects of radiation and buify coat cells on establishment of chimerism. After limited field radiation there is little evidence of residual host cells, while after cyclophosphamide alone mixed chimerism with late marrow failure can be observed.27 It may be that residual host cells suppress donor lymphocytes, an effect that can be partially overcome by infusing additional buify coat cells. Late effects of radiation and chronic GVHD are well documented in animal models28 and, in the absence of convincing evidence for superior survival, radiation probably should not be recommended for good risk patients (ie, those transplanted early without multiple pretransplant transfusions). For patients at high risk of graft failure,16 other methods of conditioning should be investigated in prospective randomized studies.

Our second major finding is that GVHD prophylaxis with cyclosporine was associated with a higher probability of survival. This increase appeared to result from less interstitial pneumonia and less chronic GVHD. Graft failure was marginally decreased in the cyclosporine group; acute GVHD was not affected. Interestingly, these data differ from our analysis of patients with leukemia where we found no significant decrease in chronic GVHD with cyclosporine compared to methotrexate.21 The finding of decreased interstitial pneumonia with cyclosporine is consistent with prior reports from the IBMTR in aplastic anemia and leukemia.20,24

We found no evidence that adding methotrexate to cyclosporine significantly improved any of the outcomes studied. These data differ in some respects from those reported from a randomized trial comparing 24 patients given methotrexate posttransplant with 22 given combined methotrexate + cyclosporine after conditioning with cyclophosphamide without radiation.21 Patients receiving methotrexate in that study had a significantly higher risk of acute GVHD than those receiving methotrexate + cyclosporine (53% v 18%). The incidence of acute GVHD with combined methotrexate + cyclosporine in that study was similar to patients receiving the same treatment regimen in the current study (group 7, Table 2, 21%); however, the incidence of acute GVHD in the methotrexate group was higher than we observed (group 1, Table 2, 32%) and than is reported in most series. The reason for this discrepancy is not known. Combined methotrexate + cyclosporine was associated with a higher probability of survival in the randomized trial (73% v 58%); these are comparable with the probabilities of survival found for the corresponding treatment regimens in the current study (80% v 63%).

Multivariate analyses indicated that several additional patient-, disease-, and transplant-related variables correlated with survival including age, interval from diagnosis to transplant, pretransplant infection, pretransplant transfusions, and using parous or previously transfused female donors. Several of these variables were reported by us and

DISCUSSION

There were two major findings in this study. The first is that there were no significant differences in survival among pretransplant conditioning regimens when results were adjusted for patient- and disease-related variables and for GVHD prophylaxis. Although this may seem surprising, there are few data supporting the contrary. Most studies of new conditioning regimens involve relatively few subjects and do not adjust for important prognostic variables.26 For example, increased use of cyclosporine occurred when new conditioning regimens were being developed. Thus, improved survival ascribed to a new conditioning regimen may actually have resulted from use of cyclosporine. These data indicate the importance of randomized trials. Unfortunately, none are reported with the conditioning regimens we studied.

Table 5. Relative Risk of Death After HLA-Identical Sibling Bone Marrow Transplantation for Severe Aplastic Anemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Favorable</th>
<th>Unfavorable</th>
<th>Relative Risk</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis against GVHD</td>
<td>CsA</td>
<td>No CsA</td>
<td>1.58</td>
<td>&lt;.0003</td>
</tr>
<tr>
<td>Infection in week before transplant</td>
<td>No</td>
<td>Yes</td>
<td>1.52</td>
<td>&lt;.004</td>
</tr>
<tr>
<td>Parous or transfused female donor</td>
<td>No</td>
<td>Yes</td>
<td>1.79</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Age of patient (n = increment in age in yr)</td>
<td>Younger</td>
<td>Older</td>
<td>1.02*</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Transfusions pre-transplant</td>
<td>&lt; 20</td>
<td>20 or more</td>
<td>1.51</td>
<td>&lt;.006</td>
</tr>
<tr>
<td>Interval diagnosis to transplant</td>
<td>&lt; 1 mo</td>
<td>1 mo or more</td>
<td>1.64</td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>

Abbreviation: CsA, cyclosporine.
others in prior studies. In this study, we show that these effects are independent of conditioning regimen and GVHD prophylaxis.

Results of transplants in aplastic anemia improved over the last 10 years. This progress has been ascribed to improved conditioning regimens and use of methotrexate + cyclosporine. The data we reviewed suggest that the progress results predominantly from using cyclosporine rather than methotrexate to prevent GVHD. Other factors, such as age, pretransplant infections, transfusion practices, donor selection, and earlier transplants contribute to improved results. Our study underscores the need for randomized controlled trials to assess new therapies in bone marrow transplantation.

REFERENCES


23. Atkinson K, Horowitz MM, Gale RP, Van Bekkum DW,


Bone marrow transplantation for severe aplastic anemia: influence of conditioning and graft-versus-host disease prophylaxis regimens on outcome

E Gluckman, MM Horowitz, RE Champlin, JM Hows, A Bacigalupo, JC Biggs, BM Camitta, RP Gale, EC Gordon-Smith and AM Marmont

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