Bone Marrow Transplantation (BMT) in Europe for Primary Immunodeficiencies Other Than Severe Combined Immunodeficiency: A Report From the European Group for BMT and the European Group for Immunodeficiency


Bone marrow (BM) transplantations performed between 1977 and 1991 at 13 European centers in 149 patients with 11 different primary immunodeficiency (ID) diseases (excluding severe combined immunodeficiency) were analyzed retrospectively. Overall survival among recipients of HLA genetically identical BM (n = 56) was 68%. Since October 1985, the date of a previous survey, a significant improvement in survival has been achieved in most ID diseases (overall survival, 81.5% ± 51.7%; P < .01), primarily because of a decrease in the frequency of infectious complications. In long-term survivors, disease correction is excellent, with minimal sequelae in most patients. In 22 patients who received closely matched BM (ie, from phenotypically identical related donors, matched unrelated donors, or one HLA-ag-mismatched related donors), the survival rate (45.5%) was not significantly better than among 71 recipients of BM with 2 or 3 mismatched HLA antigens (38%). In the latter group, favorable outcome was associated with younger age, with transplantation since October 1985 (47% vs 25%; P < .0001), and with a diagnosis of leukocyte adhesion deficiency. The improvement in outcome was mainly because of a higher engraftment rate and a decrease in the frequency of infections, although Epstein-Barr virus-induced B-lymphocyte proliferative disorders occurred in 16 patients (mainly those with Wiskott-Aldrich syndrome), 10 of whom died. The improvement in engraftment corresponded to the introduction of treatment in vivo with anti-LFA-1 antibody to prevent rejection of T-cell-depleted grafts (74% engraftment and 45% survival in 38 treated patients versus 37.5% and 21%, respectively, in 24 untreated patients).

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Bone marrow transplantation (BMT) has been developed during the last 24 years as a treatment for several lethal immunodeficiencies (IDs) involving T cells and phagocytes.1-9 Donors were initially HLA-identical, but matched unrelated or partially mismatched related individuals have also served as donors in more recent years after successes in the treatment of severe combined immunodeficiency (SCID).10-14 In a first European survey published in 1986, we described the results of BMT in 53 patients with IDs other than SCID.11 We have now retrospectively analyzed the results in a further 96 patients transplanted since October 1986 and the follow-up data on the previously reported patients. The aims were to evaluate changes in the outcome of HLA-identical and -nonidentical BMT and to identify prognostic factors.

PATIENTS AND METHODS

Between April 1973 and March 1991, 149 patients underwent BMT in 13 European centers for IDs other than SCID. Data were collected from members of the European group for BMT and the European Group for Immunodeficiency for all patients transplanted during this period. The analysis was performed on data available as of March 1, 1992, giving a minimum follow-up of 1 year. The diagnoses of the 149 patients are given in Table 1, based on the recommendations of the World Health Organization Committee for Immunodeficiencies as used previously.11 Patients with SCID were excluded; the outcome of SCID patients transplanted before March 1, 1989 has been reported elsewhere.14 There were 98 male and 51 female patients. Age at BMT ranged from 1 month to 16 years.

Donor/recipient HLA compatibility and donor origin are indicated in Table 1. BMT was performed according to the protocols applied in the participating centers. All patients except for 12 received a conditioning regimen consisting of chemotherapy (usually a combination of busulfan and cyclophosphamide); total body irradiation (TBI) was used in 12 cases. The 149 patients received a total of 171 transplants. T-cell depletion of the BM was performed in 2 HLA-identical BMT, in 3 cases involving matched unrelated donors (MUD), and in 88 HLA-mismatched BMT. Methods included albumin gradient separation and E-rosetting, E-rosetting alone, soybean agglutinin treatment and E-rosetting, and monoclonal antibodies and complement (Campath 1 M, anti-CDw52; G. Hale, Cambridge, UK). In 1986, it was agreed for HLA-nonidentical BMT that the BM sample contained no more than 4 × 10^7 nucleated cells/kg with less than 5 × 10^7 T cells/kg after T-cell depletion. In these cases, there was no post-BMT graft-versus-host disease (GVHD) prophylaxis, except in recipients of E-rosette-depleted BM who received cyclosporin for 60 days. GVHD prophylaxis, after HLA-identical non-T-cell-depleted BMT, consisted of either

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Survival analysis was comparisons was with I HLA antigen (ag) mismatch donors recipients of BM from phenotypically HLA-identical related donors. Statistical analysis could be performed given the numbers of according to diagnosis are shown in Fig 1 and Table 2, respectively. The success rate for HLA genetically identical graft recipients was significantly better than for those transplanted before 1986. Survival of recipients who received BM from a relative with HLA class II deficiency, who, if transplanted before 1986, had a significant impact on survival (Table 3). The probability of disease-free survival and the outcome according to the date of transplantation since October 1985 did not show any further improvement (data not shown).

To determine why there has been a significant improvement over time, the frequency of the main complications of BMT were evaluated in the two time periods. As shown in Table 4, there was a trend towards a reduction in infectious complications, especially after HLA-identical BMT but also after nonidentical BMT, although none of the items reached statistical significance. This reduction was associated with a decrease in the number of infection-related deaths (Table 5). B-lymphocyte proliferative disorder (BLPD) was a major complication of HLA-nonidentical transplants. It occurred in 16 patients, all of whom underwent T-cell-depleted BMT, and caused death in 10. The main risk factor was Wiskott-Aldrich syndrome (WAS); 11 of 25 patients with WAS developed BLPD, and 7 died; whereas 5 of 44 patients with other IDs developed BLPD, 3 of whom died ($P < .002$). Graft failure occurred in 38% of patients transplanted with T-cell–depleted HLA-nonidentical BM. This was the main cause of treatment failure, because survival of HLA-identical and nonidentical transplant recipients was identical when graft failure was excluded (data not shown). The engraftment rate of HLA-nonidentical BM improved with time (Table 4), because of the more frequent use of anti-LFA-1 antibody. In patients thus treated ($n = 38$), the engraftment rate was 74.3% and the survival rate was 44.7% versus 37.5% and 20.8%, respectively, in the 24 recipients of T-cell–depleted nonidentical BM who were not treated with anti-LFA-1 antibody ($P < .0001$ for engraftment and $P < .05$ for survival; patients with leukocyte adhesion deficiency [LAD] were excluded from this analysis).

The improvement was especially marked for patients who received BM from a relative with 3 HLA ag mismatches; 18 of 40 were successfully transplanted, compared with only 1 of 14 before October 1985 ($P < .0001$). Analysis of outcome according to the date of transplantation since methotrexate, cyclosporin A, or a short course of methotrexate plus cyclosporin A. GVHD was evaluated with standard criteria. Chimerism was determined by red blood cell antigen determination, by karyotyping, by HLA typing, and, more recently, by Southern blot hybridization using VNTR probes.

Differences in the observed distribution were analyzed with the $\chi^2$ test. Survival analysis was performed by the product-limit method, and comparisons of survival distribution by the log rank test. Student’s $t$-test was used to compare differences in quantitative data.

**RESULTS**

The probability of disease-free survival and the outcome according to diagnosis are shown in Fig 1 and Table 2, respectively. The success rate for HLA genetically identical BMT was similar in the different IDs, except in patients with HLA class II deficiency, who, if transplanted before 1986, did poorly, and in the few patients grafted for purine nucleoside phosphorylase (PNP) deficiency. The cure rate among recipients of BM from genetically identical siblings was higher than that among other patients. Survival of recipients of BM from phenotypically HLA-identical related donors (4 of 9), from MUD (2 of 6), from related donors with 1 HLA antigen (ag) mismatch (4 of 7) or 2 HLA ag mismatches (8 of 17), and from haplotype-mismatched related donors (19 of 54) did not appear different, although no statistical analysis could be performed given the numbers of patients in each group. As noted previously, age at BMT had a significant impact on survival (Table 3). As shown in Table 3, survival of patients transplanted after October 1985 was significantly better than for those transplanted before this date. The improvement was especially marked for patients who received BM from a relative with 3 HLA ag mismatches; 18 of 40 were successfully transplanted, compared with only 1 of 14 before October 1985 ($P < .0001$). Analysis of outcome according to the date of transplantation since methotrexate, cyclosporin A, or a short course of methotrexate plus cyclosporin A. GVHD was evaluated with standard criteria. Chimerism was determined by red blood cell antigen determination, by karyotyping, by HLA typing, and, more recently, by Southern blot hybridization using VNTR probes.

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Equivalent rates of HLA-identical BM engraftment (97%, 93%, and 100%, respectively) were obtained with the following conditioning regimens: busulfan (total dose, 16 mg/kg) and cyclophosphamide (total dose, 200 mg/kg) alone or combined with VP16 (total dose, 900 mg/m²) for some phagocyte disorders, ie, LAD, Chediak-Higashi syndrome, and familial hemophagocytic lymphohistiocytosis (FHL), and TBI (usually 8 Gy) plus cyclophosphamide (total dose, 120 mg/kg). Whereas the first two gave relatively high survival rates (71.5% and 67%, respectively), the latter was associated with poorer survival (36.5%). Regimens used before 1986, including busulfan (total dose, 8 mg/kg) and cyclophosphamide (200 mg/kg), were less efficient, because the engraftment rate was only 62%. A total of 21 patients received second transplants; 5 of the 7 who received repeat transplants from HLA-identical donors were cured compared with 5 of 14 who received non-identical BM. There were 5 survivors among the 9 patients who twice received

### Table 2. Outcome of BMT According to Disease and Incompatibility

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA Genetically Identical</th>
<th>HLA Phenotypically Matched (related and unrelated) or PMRD (1 HLA antigen)</th>
<th>PMRD (≥2 HLA antigens)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAS</td>
<td></td>
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<tr>
<td>T-cell deficiencies</td>
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<tr>
<td>Omerin's syndrome</td>
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<tr>
<td>HLA class II deficiency</td>
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<td>PNP</td>
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<td></td>
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<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Phagocytic cell disorders</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CGD</td>
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<td></td>
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<tr>
<td>Agranulocytosis</td>
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<td></td>
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<tr>
<td>LAD</td>
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<tr>
<td>Chediak-Higashi</td>
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<tr>
<td>FHL</td>
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<tr>
<td>Albinism with ID</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>22</td>
<td>71</td>
</tr>
</tbody>
</table>

* Alive with functional graft (1-year survival).
Table 3. Survival According to Date of Transplantation

<table>
<thead>
<tr>
<th>Date of BMT</th>
<th>HLA Identical Percentage Alive*</th>
<th>HLA Phenotypically Matched (related and unrelated) Percentage Alive*</th>
<th>PMRD (≥2 HLA ag) Percentage Alive*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10/85</td>
<td>29 / 52</td>
<td>7 / 14.3</td>
<td>20 / 15</td>
</tr>
<tr>
<td>≥ 10/85</td>
<td>27 / 81.9</td>
<td>15 / 60</td>
<td>51 / 47</td>
</tr>
</tbody>
</table>

* One-year survival with functional graft.

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16 mg/kg busulfan or TBI plus 16 mg/kg busulfan. Of 14 patients who underwent a second HLA-nonidentical BMT, 4 died early.

Acute GVHD ≥ grade II developed in 31% of patients who underwent HLA-identical BMT. Methotrexate alone, cyclosporin A alone, or a short course of methotrexate plus cyclosporin A were associated with similar rates of acute GVHD (37.5%, 21%, and 32.5% in 10, 15, and 15 procedures, respectively). Acute GVHD ≥ grade II developed in 31% of T-cell–depleted HLA-nonidentical BMT recipients. Chronic GVHD occurred after 12% of HLA-identical procedures, 41.7% of 1 HLA-ag-mismatch procedures, and 35.5% of 2 or 3 HLA-mismatch procedures; it resolved in all but 2 cases.

Finally, among the long-term survivors, 36 of 37 recipients of HLA genetically identical BM fully recovered from the underlying ID; disease occurred in 1 case of FHL because the donor was also affected.19 Correction was also achieved in 9 of 10 recipients of closely matched BM and in 20 of 27 recipients of 2 or 3 HLA-ag-mismatch BM. In the other cases, the correction of the ID was only partial (mainly persistent B-cell deficiency requiring Ig substitution). Chimerism was full in 9 of 10 recipients of closely matched marrow and in 13 of 27 recipients of 2 or 3 HLA-ag-mismatch marrow. In all cases in which a mixed chimerism was detected, the latter was repeatedly found over years of follow-up, although percentages of donor-derived cells could vary from 15% to 90% of leukocytes (maximal variation in 1 patient, 15% to 60% of donor-derived cells). Of 73 patients, 10 had sequelae, which were disease-related in 2 and BMT-related in 8 (chronic hepatitis C in 1, growth impairment in 3, chronic GVHD in 2, neurologic sequelae of meningitis in 1, and cerebral venous thrombosis in 1).

DISCUSSION

This European survey of BMT for primary IDs excluding SCID indicates that there has been a significant improvement in the results of HLA genetically identical procedures in a variety of IDs, relative to a previous analysis.11 This holds true for T-cell deficiencies, including HLA class II deficiency, which used to be associated with high morbidity caused by viral infections, but not for PNP deficiency.10,11 On a larger scale, these results confirm reports from several centers on results of BMT in WAS (8 of 8 and 9 of 10 successes in Rimm and Rappeport21 and Brochstein et al.,22 respectively), Omenn’s syndrome (1 of 1 in Junker et al.23), and chronic granulomatous disease (CGD; 3 of 3 successes).23,24 Our results clearly show that improved survival relates to reductions in both the incidence and the severity of all types of infection after BMT. New antimicrobial drugs and possibly better selection of patients, as well as better control of infections before and after BMT, may be responsible. A survey of patients transplanted more than 5 years ago shows stable engraftment and correction of the underlying...

Table 4. Frequency of BMT Complications (%) and Event-Free Survival (%) According to Date of Transplantation

<table>
<thead>
<tr>
<th>HLA Identical BMT*</th>
<th>HLA Nonidentical BMT†</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td></td>
</tr>
<tr>
<td>Graft failure</td>
<td></td>
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<tr>
<td>Acute GVHD ≥ grade II</td>
<td></td>
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<tr>
<td>IP</td>
<td></td>
</tr>
<tr>
<td>Bacterial and fungal infections</td>
<td></td>
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<tr>
<td>BLPD</td>
<td></td>
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<tr>
<td>Alive</td>
<td></td>
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</table>

Abbreviations: IP, interstitial pneumonitis.

* Includes HLA genetically identical siblings, HLA identical related, and matched unrelated donors.
† Includes related 1, 2, or 3 HLA-ag-mismatched donors.
ing ID, together with a low frequency of BMT-related sequelae. This favorable outcome is clearly associated with the ability to avoid TBI in these transplants, with busulfan at the dosage now used apparently avoiding serious toxicity during the 10 years of follow-up, so far. A number of long-term survivors of BMT show mixed but stable chimerism not impairing the correction of the underlying disease. Mixed chimerism was also previously found in patients transfused for diseases characterized by lymphocytic and histiocytic infiltration, such as Chediak-Higashi syndrome, FHL, and ID with partial albinism.5,7,11,19 Stability of mixed chimerism was observed for a time period of up to 11 years. The generally favorable outcome of HLA genetically identical BMT for IDs should not overshadow the fact that some patients still die. In particular, patients with PNP deficiency respond poorly to BMT,26 and the procedure is less effective in older patients. In addition, no improvement has been achieved in the prevention of acute GVHD, despite more common use of methods known to reduce this complication in other settings.16 This again underlines the need for early BMT in children with primary ID diseases and an HLA genetically identical donor.

In the last few years, the use of alternative donors has been developed for recipients who lack HLA-identical siblings.27 In this survey, we divided these procedures according to degree of incompatibility into closely matched and mismatched BMT. To our surprise, there was no difference in outcome between the two groups. This is similar to results of BMT performed for SCID,14 but contrary to BMT for leukemia aplastic anemia and osteopetrosis (Beatty et al,28 Anasetti et al,29 and B. Gerritsen et al, submitted). However, the number of patients remains quite small; therefore, the results should be interpreted with caution. Indeed, there have been several recent reports of favorable results with closely matched BM (especially from MUD) in patients with WAS (7 of 8 successes),30,31 Chediak Higashi syndrome (2 of 2 successes),30 and CGD (2 of 2 successes).32,33 It is worth noting that until March 1991, only 6 MUD transplants for patients with ID diseases other than SCID had been reported to the European registry.

However, the results of this survey do show a marked improvement in the results of haplotype-mismatched BMT since October 1985. There are few reports of these procedures in ID patients, and most are disappointing, eg, 5 of 6 failures in WAS patients treated by Brochstein et al.21 However, Rumelhardt et al33 described successes with haploidentical T-cell–depleted BMT in 3 of 4 patients with WAS. Factors associated with a favorable outcome of haploidentical BMT in this survey were T-cell depletion, young age, transplants performed in recent years, diagnosis of LAD, or use of monoclonal antibodies to prevent graft rejection. The few attempts at haploidentical BMT without T-cell depletion (n = 3) led to death from GVHD. Progress in recent years is in part related to improvements in the control of infections, as in the case of HLA genetically identical BMT (see above), although the infection-related death rate remains high. Of note is the frequency of EBV Epstein-Barr virus (EBV)-associated BLPD, a complication primarily associated with WAS. This may reflect both the older age of these patients, as compared with other ID patients, and the poor control of EBV replication in WAS patients, as exemplified by rare cases of EBV-induced BLPD in WAS patients before BMT.31 This is confirmed by the occurrence of BLPD in 3 of 6 WAS recipients of T-cell–depleted haploidentical BM in another series.31

The engraftment rate has improved in the last few years with the use of anti–LFA-1 antibody infusion to prevent rejection. A report of the corresponding European trial has been published elsewhere.34 Further follow-up and inclusion of FHL patients confirm this observation, as do the excellent results of haploidentical BMT in LAD patients. It is remarkable that survival after haploidentical BMT is not significantly different from that after HLA genetically identical BMT, if graft failures are excluded. This emphasizes that the latter complication remains the major obstacle to this form of BMT, even though improvements have been made. It is also important to note that haploidentical BMT in anti–LFA-1–treated patients and in patients with LAD led to stable engraftment and disease correction (follow-up of at least 1 year after BMT), except in one case. However, the kinetics of functional immune recovery are much slower, as compared with HLA-identical BMT, and are also occasionally incomplete. For all these reasons, haploidentical BMT remains an investigational procedure reserved for experienced centers applying evaluable protocols and for patients with immediately life-threatening complications.30,35

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