Successful Engraftment of T-Cell-Depleted Haploidentical “Three-Loci” Incompatible Transplants in Leukemia Patients by Addition of Recombinant Human Granulocyte Colony-Stimulating Factor–Mobilized Peripheral Blood Progenitor Cells to Bone Marrow Inoculum

Patients who undergo transplantation with haploidentical “three-loci” mismatched T-cell–depleted bone marrow (BM) are at high risk for graft failure. To overcome the host-versus-graft barrier, we increased the size of the graft inoculum, which has been shown to be a major factor in controlling both immune rejection and stem cell competition in murine models. Seventeen patients (mean age, 23.2 years; range, 6 to 51 years) with end-stage chemotherapy-refractory leukemia were received transplants of a combination of BM with recombinant human granulocyte colony-stimulating factor–mobilized peripheral blood progenitor cells from HLA-haploidentical “three-loci” incompatible family members. The average concentration of colony-forming unit–granulocyte-macrophage in the final inoculum was sevenfold to 10-fold greater than that found in BM alone. The sole graft-versus-host disease (GVHD) prophylaxis consisted of T-cell depletion of the graft by the soybean agglutination and E-rosetting technique. The conditioning regimen included total body irradiation (TBI) in a single fraction at a fast dose rate, antithymocyte globulin, cyclophosphamide and thiotepa to provide both immunosuppression and myeloablation. One patient rejected the graft and the other 16 had early and sustained full donor-type engraftment. One patient who received a much greater quantity of T lymphocytes than any other patient died from grade IV acute GVHD. There were no other cases of GVHD >grade II. Nine patients died from transplant-related toxicity, 2 relapsed, and 6 patients are alive and event-free at a median follow-up of 230 days (range, 100 to 485 days). Our results show that a highly immunosuppressive and myeloablative conditioning followed by transplantation of a large number of stem cells depleted of T lymphocytes by soybean agglutination and E-rosetting technique has made transplantation of three HLA-antigen disparate grafts possible, with only rare cases of GVHD.

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Table 1. Patient's Characteristics and Donor-Host Relationship

<table>
<thead>
<tr>
<th>UPN</th>
<th>Age/Sex</th>
<th>Disease</th>
<th>Status</th>
<th>Age/Sex</th>
<th>Relationship</th>
<th>Donor HLA Analysis</th>
<th>Host HLA Analysis</th>
</tr>
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<tbody>
<tr>
<td>306</td>
<td>22/M</td>
<td>AML</td>
<td>REL</td>
<td>45/M</td>
<td>Father</td>
<td>A2B35DR4</td>
<td>A2B35DR4</td>
</tr>
<tr>
<td>313</td>
<td>37/M</td>
<td>AML</td>
<td>REL</td>
<td>67/F</td>
<td>Mother</td>
<td>A1B7DR2</td>
<td>A2B49DR6</td>
</tr>
<tr>
<td>315</td>
<td>17/M</td>
<td>ALL</td>
<td>REL</td>
<td>40/F</td>
<td>Mother</td>
<td>A2B35DR11</td>
<td>A2B35DR11</td>
</tr>
<tr>
<td>317</td>
<td>31/F</td>
<td>ALL</td>
<td>REL</td>
<td>39/M</td>
<td>Brother</td>
<td>BLB8DR4</td>
<td>A2B18DR4</td>
</tr>
<tr>
<td>319</td>
<td>15/M</td>
<td>CML</td>
<td>BT</td>
<td>49/F</td>
<td>Mother</td>
<td>A2B35DR11</td>
<td>A2B35DR3</td>
</tr>
<tr>
<td>320</td>
<td>22/M</td>
<td>CML</td>
<td>BT</td>
<td>44/F</td>
<td>Mother</td>
<td>A2850DR11</td>
<td>A2B49DR7</td>
</tr>
<tr>
<td>321</td>
<td>26/M</td>
<td>AML</td>
<td>REL</td>
<td>30/M</td>
<td>Brother</td>
<td>A32B18DR7</td>
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</tr>
<tr>
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<td>6/M</td>
<td>ALL</td>
<td>REL</td>
<td>33/M</td>
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<td>A1B35DR6</td>
<td>A2B35DR11</td>
</tr>
<tr>
<td>331</td>
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<td>CML</td>
<td>BT</td>
<td>45/F</td>
<td>Mother</td>
<td>A2B49DR11</td>
<td>A2B49DR53</td>
</tr>
<tr>
<td>333</td>
<td>23/M</td>
<td>ALL</td>
<td>REL</td>
<td>19/M</td>
<td>Brother</td>
<td>A2B39DR11</td>
<td>A2B39DR11</td>
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<tr>
<td>334</td>
<td>51/F</td>
<td>ALL</td>
<td>REL</td>
<td>55/F</td>
<td>Sister</td>
<td>A2B39DR11</td>
<td>A2B39DR11</td>
</tr>
</tbody>
</table>

Abbreviations: BT, blastic transformation; REL, relapse; BL, blank.

ing to the T-cell-depleted BM PBPCs obtained from the donor after the administration of rhG-CSF. These cells were subjected to the same T-cell-depletion procedure. No post-grafting immunosuppressive treatment was administered.

MATERIALS AND METHODS

Patients. Seventeen patients (15 men and 2 women; median age, 23.2 years; range, 6 to 51 years) with advanced chemoresistant leukemia (5 acute myeloid leukemia [AML], 9 acute lymphoblastic leukemia [ALL], and 3 chronic myeloid leukemia in blastic phase) received transplants between March 1993 and March 1994. All patients received grafts from HLA-haploidentical "three-loci" incompatible family members. Six donors were siblings and 11 were parents (Table 1). Antidonor lymphocyte antibodies, as assayed in a complement-dependent microcytotoxicity crossmatch test, were not detected in any of the 12 evaluated cases.

According to the guidelines established by the Umbria Region Public Health Service ethical committee, written informed consent was obtained from patients or their parents as well as from the donors.

Conditioning regimen. All patients received 8 Gy TBI in a single fraction at a fast dose rate (16 cGy/min midplane) from an 18-MV photon beam linear accelerator on day −5. Lungs were shielded by individual lead moulds; the corrected mean total lung dose was 7 Gy. Thiopeta (10 mg/kg) was administered intravenously (IV) in two divided doses (4 hours for each infusion) on day −4. From days −4 to −1, 5 mg/kg rabbit ATG (Fresenius AG, Oberursel, Germany) was infused over 8 hours, followed by 60 mg/kg cyclophosphamide on days −3 and −2. No immunosuppressive therapy was administered as GVHD prophylaxis after transplant.

Supportive care. Patients were cared for in laminar air-flow rooms until the neutrophil count recovered to 1 × 10⁹/L. All patients received prophylactic trimethoprim-sulfamethoxazole for Pneumocystis carinii, ciprofloxacin for selective gut decontamination, fluconazole for fungal prophylaxis, Ig (0.5 g/kg/wk from day −5 to day +90), and total parenteral nutrition. Fever during the period of neutropenia was treated with broad-spectrum antibiotics; amphotericin B was added if fever persisted. Cytomegalovirus (CMV) prophylaxis consisted of ganciclovir (10 mg/kg/d from day −6 to day −2 and resumed at 5 mg/kg/d from day +7 to day +21, followed by maintenance treatment with 5 mg/kg thrice weekly until day +90). Foscarnet (90 mg/kg/d) was administered from day −1 to day +10. All but 1 patient (UPN 306) received G-CSF (5 μg/kg/d) for a mean of 4.7 days (range, 2 to 9 days) in the immediate posttransplant phase.
All blood products were filtered and irradiated before infusion.

**Engraftment and immunologic studies.** Time to engraftment was assessed by determining the day after transplant on which patients achieved 0.5 x 10^9 neutrophils/L and 25 x 10^9 platelets/L independent of transfusion support. Chimerism was assessed by karyotyping of PB lymphocytes and the analysis of restriction fragment length polymorphism (RFLP) in both PB and BM. The degree of acute GVHD was assessed using standard clinical criteria.

Posttransplant lymphoid cell subsets were identified by two-color immunofluorescence and flow cytometry. Cytotoxicity against a panel of natural killer (NK)-cell-sensitive and -resistant targets was evaluated by a 51-Cr release assay as described. T-cell proliferation was assessed by stimulating cells with anti-CD3 MoAb and pulsing the cultures with [H]-thymidine for 12 hours at the end of a 72-hour culture period. For detection of interleukin-2 (IL-2) activity in culture supernatants, the CTLL murine cell line assay was used.

BM and PB mononuclear cell (PBMC) collection. Donor BM cells were obtained under general anesthesia by multiple aspirations from the iliac crests bilaterally and cryopreserved, as described below. rhG-CSF (12 μg/kg/d) was administered to donors by continuous subcutaneous infusion from 24 hours after BM harvesting and continued for 5 to 7 days. Two to four leukaphereses were performed between days 4 and 7 in the first 7 donors, who received rhG-CSF for 6 to 7 days; whereas the remaining 10 donors, who were treated with rhG-CSF for 5 to 6 days, underwent two to three leukaphereses (days 4, 5, and 6).

The donors reported no untoward effects during or after the administration of rhG-CSF or from the blood collection.

**BM and PBPC processing.** All BM preparations were depleted of T lymphocytes using the soybean agglutination and E-rosetting technique, as previously described. This procedure results in a 3- to 3.5-log reduction in the number of T lymphocytes. Depletion of T lymphocytes from the PBMCs in the first 7 cases was achieved by two-step E-rosetting procedure, whereas the combined soybean agglutination and E-rosetting technique was used in the last 10 cases. Aliquots were taken for differential cell counts, MoAb staining, and GFU-GM assay at each stage of processing. T-cell-depleted BM and PB cells were frozen in a controlled rate liquid nitrogen freezer and stored in the vapor phase of liquid nitrogen. In some cases, the collections from PB were performed on the day before and on the day of the transplant; these cells were not cryopreserved.

CFU-GM were measured in whole blood and in the leukapheresis product by plating 0.5 x 10^9 mononuclear cells in a 3% agar solution containing 10% of 5637 cell line conditioned medium, 20% foetal bovine serum, and Iscove medium. Colonies of greater than 40 cells were counted on an inverted microscope (Leica, Wetzlar, Germany) after 10 to 14 days.

The number of CD34^+ cells were measured both in whole blood and in the leukapheresis product with a direct immunofluorescence technique using the fluorescein conjugate HPCA-2 MoAb (Beeton Dickinson, Palo Alto, CA). Negative control was assessed using a mouse IgG1-fluorescein isothiocyanate (FITC). Cells were analyzed on a Profile II (Coulter Corp, Hialeah, FL). A gate was established to include only lymphocytes and mononuclear cells. Ten thousand cells were evaluated.

Results

**Mobilization and collection of PBPCs.** In the normal donors, under steady-state hematopoiesis (baseline), minimal amounts of circulating CD34^+ cells (median, 0.5/L blood; range, 0 to 15/µL) and CFU-GM (median, 122.7/mL; range, 0 to 268/mL) were detectable. With G-CSF treatment, the donor white blood cell count increased from a median of 6.7 x 10^9/L to 72 x 10^9/L by day 7.

Peak levels of CD34^+ cells, as well as of CFU-GM, were reached simultaneously at a median of 5 days. Median values of peak levels were 830.7 CD34^+ cells/µL (range, 92.8 to 1,035 CD34^+ cells/µL) and 12,347 CFU-GM/mL (range, 549 to 20,126 CFU-GM/mL).

The two to four leukapheresis procedures yielded a mean total number of 10.4 x 10^9 mononuclear cells/kg of donor body weight (range, 4 to 23 x 10^9 mononuclear cells/kg). The combined leukapheresis products contained a mean of 11.62 ± 4.74 x 10^9/kg CD34^+ cells (range, 5.47 to 18.99 x 10^9/kg CD34^- cells) and 73,182 ± 40.8 x 10^9/kg CFU-GM (range, 13 to 132,53 x 10^9/kg CFU-GM).

**T-cell depletion of BM and PBMCs.** Table 2 reports the mean number (per kilogram of body weight) of mononuclear cells, CFU-GM, CD34^+ cells, and CD3^+ cells present in BM, PB, and the combined products administered to the patients after T-cell depletion.

**Engraftment.** One patient (UPN 331) rejected the graft on posttransplant day 18 after initial myeloid engraftment. RFLP analysis of granulocytes confirmed that they were donor-derived on day 14 (data not shown). This early rejection was associated with the abrupt emergence of host T cells that exhibited donor-specific cytotoxic reactivity.

The other 16 patients had early and sustained engraftment. They achieved PB neutrophil counts greater than 0.5 x 10^9/L and greater than 1.0 x 10^9/L at a mean of 10.2 days (range, 9 to 17 days) and 11.5 days (range, 10 to 22 days), respectively. Platelet counts of 25 x 10^9/L and 50 x 10^9/L were reached at a mean of 17.2 days (range, 10 to 29 days) and 30 days (range, 14 to 60 days), respectively. The time course of engraftment is illustrated in Fig 1.

The curves represent the time required for T-cell-depleted "three-loci" incompatible transplants to reach 0.5 and 1.0 x 10^9/neutrophils/L, compared with our own historical control group of 23 patients who received autologous chemotherapy/cytokine-mobilized PBPCs (Tahilu et al, unpublished observations, 1994) and 93 patients receiving transplants of T-cell-depleted HLA genotypically identical BM cells. RFLP analysis documented full donor-type chimerism in both the PB and BM of the 16 engrafted patients (data not shown).

**Immune reconstitution.** Phenotypic and functional analyses of posttransplant lymphocyte subsets were performed and compared with those obtained in HLA-matched T-cell-depleted BM recipients. Whereas essentially identical data were obtained for B-cell and T-cell subsets in the two BM settings (data not shown), a twofold increase in the early (1 to 2 months postgrafting) NK cell wave was noted in mismatched as compared with matched transplants. The
Table 2. Characteristics of Transplanted BM and PB Cells After T-Cell Depletion

<table>
<thead>
<tr>
<th>Group</th>
<th>BM</th>
<th>Total</th>
<th>BM</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>MNC ($\times 10^6$/$kg$)*</td>
<td></td>
<td>MNC ($\times 10^6$/$kg$)</td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>0.31</td>
<td>5.96</td>
<td>6.27</td>
<td></td>
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<tr>
<td>Group II</td>
<td>0.27</td>
<td>2.98</td>
<td>3.25</td>
<td></td>
</tr>
<tr>
<td>CFU-GM ($\times 10^9$/$kg$)</td>
<td>12.77</td>
<td>71.55</td>
<td>84.32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.56</td>
<td>35.80</td>
<td>40.36</td>
<td></td>
</tr>
<tr>
<td>CD34+ ($\times 10^6$/$kg$)</td>
<td>13.9</td>
<td>5.91</td>
<td>6.23</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>2.14</td>
<td>1.24</td>
<td>1.43</td>
<td></td>
</tr>
</tbody>
</table>

For group I, (7 donors), BM was T-cell-depleted by SBA and one-step E-rosette. BMCs were T-cell-depleted by only two-step E-rosette. Donors underwent two to four leukaphereses. For group II (10 donors), BM and PBMCs were T-cell-depleted by SBA and two-step E-rosette. Donors underwent two to three leukaphereses.

Abbreviation: ND, not determined.

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in unmanipulated BM help to eliminate or inactivate the BM inoculum that these host cells can survive, because donor T cells transplants has been an increase in the incidence of graft pathogenesis of graft failure, clinical and experimental data strongly indicate that ang the preparative regimen.44 In the hope of eliminating residual rapid-release T lymphocytes and thereby promoting sustained engraftment, attempts have been made to employ more intensive pretransplant immunosuppression. Various approaches, such as TBI in a single fraction at a fast dose rate, addition of total lymphoid irradiation (TLI) to TBI,45 treatment of the recipient with anti-T MoAbs45,46 or ATG, addition of cytosine arabinoside47 or thiopeta (Aversa et al, unpublished observations, 1992) to pretransplant conditioning, have generally been unsuccessful in preventing rejection of T-cell–depleted grafts with high degrees of HL A disparity.

Early studies in rodents using unseparated marrow, although complicated by lethal GVHD, have shown that transplants of mismatched marrow could engraft if a larger BM inoculum was used compared with doses required for syngeneic transplants.48 Likewise, it has been shown subsequently in a mouse model that, when a certain degree of immunosuppression is achieved by the conditioning regimen, the number of donor BM cells (depleted of T lymphocytes) is a critical determinant for engraftment.49 In our study a 7- to IO-fold increase in the dose of the transplant inoculum was followed by prompt and sustained reconstitution of hematopoiesis whereas complicated by lethal GVHD, the effect of which could be translated to its actual equivalence in cell dose. Furthermore, even when graduated numbers of host type T cells were added back to heavily conditioned recipients of BM allografts, it has been possible to overcome the allo-responses mounted by these cells against the graft by increasing the size of the T-cell–depleted transplant.51 Similarly, the effect of both donor cells in mismatched transplants of mismatched marrow has been studied. The very large cell dose we infused after the intensive conditioning regimen was followed by prompt and sustained engraftment in 16 of 17 recipients of haploidentical ‘‘three-loci’’ mismatched T-cell–depleted BM. Neutrophil and platelet recovery was very rapid and the engraftment characteristics were very similar to those observed in syngeneic

<table>
<thead>
<tr>
<th>UPN</th>
<th>Disease</th>
<th>Status at Transplant</th>
<th>Blasts (%) in BM</th>
<th>Engraftment</th>
<th>Acute GVHD (grade)</th>
<th>Current Status (June 30, 1994)</th>
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<tbody>
<tr>
<td>306</td>
<td>AML</td>
<td>2nd relapse</td>
<td>80</td>
<td>Yes</td>
<td>0</td>
<td>Alive in CCR on day +485</td>
</tr>
<tr>
<td>313</td>
<td>AML</td>
<td>Induction failure</td>
<td>100</td>
<td>Yes</td>
<td>0</td>
<td>Alive in CCR on day +413</td>
</tr>
<tr>
<td>315</td>
<td>ALL</td>
<td>3rd relapse</td>
<td>100</td>
<td>Yes</td>
<td>0</td>
<td>Died on day 120 from CMV-IP</td>
</tr>
<tr>
<td>317</td>
<td>ALL</td>
<td>2nd relapse</td>
<td>100</td>
<td>Yes</td>
<td>IV</td>
<td>Died on day 60 from GVHD</td>
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<tr>
<td>319</td>
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<td>2nd blast crisis</td>
<td>80</td>
<td>Yes</td>
<td>0</td>
<td>Died on day 90 from Idiopat-IP</td>
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<tr>
<td>320</td>
<td>CML</td>
<td>3rd blast crisis</td>
<td>15</td>
<td>Yes</td>
<td>0</td>
<td>Died on day 20 from CMV-IP</td>
</tr>
<tr>
<td>321</td>
<td>AML</td>
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<td>100</td>
<td>Yes</td>
<td>0</td>
<td>Died on day 18 from CMV-IP</td>
</tr>
<tr>
<td>329</td>
<td>ALL</td>
<td>3rd relapse</td>
<td>100</td>
<td>Yes</td>
<td>0</td>
<td>Relapsed on day 60, died on day 70</td>
</tr>
<tr>
<td>331</td>
<td>CML</td>
<td>2nd blast crisis</td>
<td>30</td>
<td>No</td>
<td>NE</td>
<td>Died on day 45 from segps</td>
</tr>
<tr>
<td>333</td>
<td>ALL</td>
<td>3rd relapse</td>
<td>15</td>
<td>Yes</td>
<td>0</td>
<td>Relapsed on day 50, died on day 60</td>
</tr>
<tr>
<td>334</td>
<td>ALL</td>
<td>2nd relapse</td>
<td>15</td>
<td>Yes</td>
<td>I</td>
<td>Died on day 180 from Idiopat-IP</td>
</tr>
<tr>
<td>401</td>
<td>AML</td>
<td>3rd relapse</td>
<td>100</td>
<td>Yes</td>
<td>0</td>
<td>Died on day 45 from segps</td>
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<tr>
<td>402</td>
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<td>Induction failure</td>
<td>100</td>
<td>Yes</td>
<td>I</td>
<td>Alive in CCR on day +157</td>
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<tr>
<td>404</td>
<td>ALL</td>
<td>2nd relapse</td>
<td>100</td>
<td>Yes</td>
<td>0</td>
<td>Died on day 62 from Idiopat-IP</td>
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<tr>
<td>407</td>
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<td>2nd relapse</td>
<td>15</td>
<td>Yes</td>
<td>I</td>
<td>Alive in CCR on day +126</td>
</tr>
<tr>
<td>408</td>
<td>ALL</td>
<td>3rd relapse</td>
<td>15</td>
<td>Yes</td>
<td>I</td>
<td>Alive in CCR on day +110</td>
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<td>409</td>
<td>ALL</td>
<td>3rd relapse</td>
<td>10</td>
<td>Yes</td>
<td>I</td>
<td>Alive in CCR on day +100</td>
</tr>
</tbody>
</table>

Abbreviations: NE, not evaluable; CCR, continuous complete remission; IP, interstitial pneumonia.
PBPC transplants\textsuperscript{19} or in our historical control group of patients who received autologous chemotherapy/rhG-CSF–mobilized PBPCs (Tabilio et al, unpublished observations, 1994). The short posttransplant course of rhG-CSF treatment may have also contributed to the swift increase in the neutrophil count. However, the patients (UPN 306 and 409) who did not receive G-CSF had a similar progression in the neutrophil count.

The impressive rate of engraftment across the most difficult histoincompatibility barrier shows that, in humans, as in mice, the stem cell dose plays a critical role in the engraftment of T-cell–depleted transplants. This concept is further supported by the finding that the same pretransplant conditioning failed to promote engraftment in any of the 5 patients receiving transplantats of conventional doses of T-cell–depleted ‘‘three-loci’’ mismatched BM cells (Aversa et al, unpublished observations, 1992).

One potential major concern raised by the use of a large T-cell–depleted inoculum is an increased risk of GVHD, mainly caused by T-cell contamination of PBPCs. However, greater than grade I GVHD was extremely rare and occurred in only 1 of the evaluable patients who received the largest number of T cells (11.3 \times 10^9, almost twofold more than the average number administered to group I and about 10-fold more than the average of group II). Kerman et al\textsuperscript{51} suggested that the threshold dose of clonable T cells that leads to GVHD is about 2 \times 10^9/kg. Considering that the cloning efficiency is around 20\%, our observed threshold falls within the same range. However, it is likely that ATG, administered between days –5 and –2, would contribute to lowering both the frequency and severity of GVHD by exerting a cytotoxic effect against donor inoculum T lymphocytes. The following points support this hypothesis: (1) the plasmatic half-life of rabbit ATG is 6 days; (2) the introduction of ATG\textsuperscript{32} or Campath\textsuperscript{53} in the conditioning regimens for mismatched transplanted has been associated with a lower incidence of severe acute GVHD.

Despite the intensive prior therapy and the high leukemic burden at the time of transplant, the transplant-related mortality was very close to those reported by the European (47\% at 2 years in CML patients in accelerated phase and 62\% in blast crisis) and Italian (62\% at 2 years in 46 advanced leukemia patients; Gruppo Italiano Trapianto Midollo Osseo, data unpublished) Registries in end-stage leukemia patients; and, therefore, contribute to lowering mortality. After the schedule of ganciclovir was modified to begin day +7, no case of CMV pneumonia was documented in the 9 patients (group II).

Given the fact that the patients in this small series received transplants while in refractory end-stage disease and that the mean follow-up is short, no conclusions can be drawn about survival. Nevertheless, the high engraftment rate, virtual elimination of acute GVHD greater than grade II, and acceptable conditioning-related toxicity suggest that this approach should be applied to selected leukemia patients who do not have HLA-matched donors.

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Successful engraftment of T-cell-depleted haploidentical "three-loci" incompatible transplants in leukemia patients by addition of recombinant human granulocyte colony-stimulating factor-mobilized peripheral blood progenitor cells to bone marrow inoculum

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