

## TREATMENT OF CHRONIC GRANULOMATOUS DISEASE WITH NONMYELOABLATIVE CONDITIONING AND A T-CELL-DEPLETED HEMATOPOIETIC ALLOGRAFT

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### ABSTRACT

**Background** The treatment of chronic granulomatous disease with conventional allogeneic hematopoietic stem-cell transplantation carries a high risk of serious complications and death. We investigated the feasibility of stem-cell transplantation without ablation of the recipient's bone marrow.

**Methods** Ten patients, five children and five adults, with chronic granulomatous disease underwent peripheral-blood stem-cell transplantation from an HLA-identical sibling. We used a nonmyeloablative conditioning regimen consisting of cyclophosphamide, fludarabine, and antithymocyte globulin. The allograft was depleted of T cells to reduce the risk of severe graft-versus-host disease. Donor lymphocytes were administered at intervals of 30 days or more after the transplantation to facilitate engraftment.

**Results** After a median follow-up of 17 months (range, 8 to 26), the proportion of donor neutrophils in the circulation in 8 of the 10 patients was 33 to 100 percent, a level that can be expected to provide normal host defense; in 6 the proportion was 100 percent. In two patients, graft rejection occurred. Acute graft-versus-host disease (grade II, III, or IV) developed in three of the four adult patients with engraftment, one of whom subsequently had chronic graft-versus-host disease. None of the five children had grade II, III, or IV acute graft-versus-host disease. During the follow-up period, four serious infections occurred among the patients who had engraftment. Three of the 10 recipients died. Preexisting granulomatous lesions resolved in the patients in whom transplantation was successful.

**Conclusions** Nonmyeloablative conditioning followed by a T-cell-depleted hematopoietic stem-cell allograft is a feasible option for patients with chronic granulomatous disease, recurrent life-threatening infections, and an HLA-identical family donor. (N Engl J Med 2001;344:881-8.)

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**C**HRONIC granulomatous disease is a rare inherited immunodeficiency disorder characterized by recurrent, often life-threatening bacterial and fungal infections and granulomas in multiple organs. The disease is due to a mutation in one of the four genes that encode the four subunits of the oxidase enzyme of phagocytes (*gp91<sup>phox</sup>*, *p47<sup>phox</sup>*, *p67<sup>phox</sup>*, and *p22<sup>phox</sup>*). This defect renders myeloid cells incapable of generating superoxide, there-

by compromising their antimicrobial activity. Standard prophylaxis against infection in patients with chronic granulomatous disease consists of treatment with interferon gamma and daily administration of antibiotics such as trimethoprim-sulfamethoxazole.<sup>1-3</sup> Despite these measures, the annual rate of death due to chronic granulomatous disease in the United States is 2 to 5 percent.<sup>4</sup> For this reason, there is a need for other, more definitive therapies for this disease.

Case reports of allogeneic hematopoietic stem-cell transplantation for chronic granulomatous disease suggest that immunocompetence may be restored with engraftment of donor stem cells.<sup>5-12</sup> However, because of the high rates of death and serious illness related to this treatment, most practitioners defer allogeneic stem-cell transplantation until the patient is chronically ill and debilitated.<sup>13</sup> New approaches to stem-cell transplantation with the use of conditioning regimens that do not ablate the recipient's bone marrow are under investigation.<sup>10,14-17</sup> The toxicity of these new conditioning regimens is less than that associated with conventional, myeloablative regimens, but the risk of graft-versus-host disease after stem-cell transplantation is similar. Donor T cells present in the stem-cell graft are the cause of graft-versus-host disease. Depletion of T cells from the graft reduces the risk of severe graft-versus-host disease but increases the risk of graft rejection.<sup>18,19</sup> However, the likelihood of rejection of a T-cell-depleted stem-cell graft is reduced by infusions of donor lymphocytes after transplantation.<sup>10,20-22</sup>

In this study, 10 patients with chronic granulomatous disease underwent transplantation of peripheral-blood stem cells from an HLA-identical sibling after undergoing a nonmyeloablative conditioning regimen. In an attempt to reduce the risk of severe graft-versus-host disease, the graft was thoroughly depleted of T cells. To reduce the risk of graft rejection, donor

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lymphocytes were infused at intervals after transplantation, according to a predetermined regimen.

## METHODS

### Patients

The characteristics of the 10 patients are listed in Table 1. Chronic granulomatous disease was confirmed by the absence of oxidase activity in neutrophils by dihydrorhodamine oxidation analysis.<sup>23,24</sup> The patients or their legal guardians gave written informed consent for enrollment in the study (National Institutes of Health protocol 98-I-0104), which was approved by the institutional review board of the National Heart, Lung, and Blood Institute. All the patients had had at least two life-threatening infections requiring intravenous antibiotic therapy but were free of infection at the time of stem-cell transplantation. Five of the patients were receiving interferon gamma therapy at the time of enrollment; the other five patients stopped interferon gamma therapy because of adverse effects (fever, headache, or fatigue) or because the patient had decided against therapy. As part of the informed-consent process, all the patients (or their guardians) were advised of the beneficial effects of a combination of interferon gamma treatment and daily antibiotics and were told that this combination is an alternative to stem-cell transplantation.

### Collection and Processing of Donor Stem Cells and T Cells

HLA matching of the donors and recipients was confirmed by molecular typing of the HLA class I and HLA class II loci. The donors received granulocyte colony-stimulating factor (filgrastim [G-CSF]) at a dose of 10  $\mu\text{g}$  per kilogram of body weight per day for six days. Leukapheresis was performed on days 5 and 6 of G-CSF administration. With the use of an immunomagnetic-bead selection system (Isolex 300i, version 2.0 or 2.5, Nexell Therapeutics, Irvine, Calif.), the apheresis product was enriched for CD34+ cells (the population that contains hematopoietic stem cells) and was depleted of T cells with use of a panel of three T-cell-specific

monoclonal antibodies (CD2, CD6, and CD7). The protocol for stem-cell purification was reviewed and approved by the Food and Drug Administration. All the depletion procedures reduced the number of T cells by a factor of 30,000 to 100,000; we therefore added T cells back to the donor graft so that it contained  $1.0 \times 10^5$  CD3+ T cells per kilogram of the recipient's body weight (Table 2). Before the administration of G-CSF, donors with adequate peripheral access (the donors for Patients 2, 4, 5, 9, and 10) underwent a leukapheresis procedure designed specifically for the collection of lymphocytes. Lymphocytes from the other donors were harvested from the G-CSF-mobilized apheresis products and then, with the use of immunomagnetic-bead selection, were enriched for CD34+ cells.

### Transplantation

Prophylactic therapy with interferon gamma was discontinued two to four weeks before the study treatment was started. Patients underwent a conditioning regimen consisting of cyclophosphamide at a dose of 60 mg per kilogram (days 7 and 6 before transplantation), fludarabine at a dose of 25 mg per square meter of body-surface area (days 5 to 1 before transplantation), and antithymocyte globulin at a dose of 40 mg per kilogram (days 5 to 2 before transplantation). Administration of cyclosporine was started on day 4 before transplantation and was continued until day 100 after transplantation (target trough level, 200 to 350  $\mu\text{g}$  per liter). Patients were infused with a minimum of  $5.0 \times 10^6$  CD34+ cells per kilogram and with exactly  $1.0 \times 10^5$  CD3+ T cells per kilogram. The presence of both donor and recipient T cells and of both donor and recipient myeloid cells in the blood (i.e., donor-recipient chimerism) was ascertained weekly. Each patient received an infusion of donor peripheral-blood lymphocytes containing  $2.0 \times 10^6$  CD3+ cells per kilogram on day 30 after transplantation if donor T cells constituted less than 60 percent of the patient's circulating CD3+ T cells. If the proportion of donor T cells was less than 60 percent on day 60 and there was no evidence of graft-versus-host disease, the patient received a second infusion of donor lymphocytes, containing  $1.0 \times 10^7$  CD3+ cells per kilogram. After the discontinuation of cyclosporine, three donor-lymphocyte infusions containing  $1.0 \times 10^7$  CD3+ cells per kilogram of the recipient's body weight were given at 90-day intervals, as long as the proportion of donor T cells in the blood remained below 60 percent. Two patients in whom donor-recipient hematopoietic chimerism persisted after the prescribed regimen of donor-lymphocyte infusions received an additional  $5.0 \times 10^7$  CD3+ cells per kilogram, given 14 months after transplantation in one patient and 11 months after transplantation in the other.

### Analysis of Chimerism

Donor and recipient cells were detected by quantitative analysis of informative microsatellite DNA sequences. Purified CD15+ neutrophils and CD3+ T cells were isolated from peripheral blood with the use of immunomagnetic beads. DNA was extracted from these cells, and seven distinct microsatellite sequences were amplified by the polymerase chain reaction (PCR) with a multiplexed PCR kit (Ampfister Cofiler or Profiler, Perkin-Elmer Applied Biosystems, Foster City, Calif.).<sup>25</sup> The PCR product was run on an automated sequencer (model 310, Perkin-Elmer Applied Biosystems) and analyzed with GeneScan software (ABI Prism, version 3.1, Foster City, Calif.). The degree of chimerism was assessed by comparing the peak areas under the curves representing the amount of PCR product amplified from donor-specific and recipient-specific microsatellite alleles. The presence of oxidase-positive neutrophils was detected by flow cytometry with the use of a dihydrorhodamine oxidation assay.<sup>23,24</sup>

## RESULTS

### Collection and Processing of Donor Stem Cells

The required minimal dose of CD34+ cells,  $5.0 \times 10^6$  cells per kilogram of the recipient's weight,

TABLE 1. CHARACTERISTICS OF THE PATIENTS.

PATIENT No.	AGE (YR)	SEX	SEX OF DONOR	MUTATION IN PHAGOCYTE OXIDASE GENE*	No. OF EPISODES OF LIFE-THREATENING INFECTION BEFORE TRANSPLANTATION†	PRESENCE OF HLA ANTI-BODIES
1	5	M	F	<i>gp91<sup>phox</sup></i>	2	No
2	25	M	F	<i>p22<sup>phox</sup></i>	15‡	No
3	18	M	F	<i>gp91<sup>phox</sup></i>	13‡	Yes
4	12	M	M	<i>gp91<sup>phox</sup></i>	4	Yes
5	10	M	F	<i>gp91<sup>phox</sup></i>	2	No
6	34	M	F	<i>gp91<sup>phox</sup></i>	8‡	No
7	8	M	M	<i>gp91<sup>phox</sup></i>	3	Yes
8	8	M	M	<i>gp91<sup>phox</sup></i>	3	No
9	36	M	F	<i>gp91<sup>phox</sup></i>	15‡	Yes
10	23	M	M	<i>p47<sup>phox</sup></i>	3	No
Median	15					
Range	5–36					

\*The presence of *gp91<sup>phox</sup>* was determined by the finding that the mother was a carrier; the presence of *p22<sup>phox</sup>* and *p47<sup>phox</sup>* was determined by Western blotting.

†Life-threatening infection was defined as infection of the lung, liver, skin, brain, or bone that required hospitalization and prolonged intravenous antibiotic therapy.

‡This value is an estimate.

**TABLE 2.** CHARACTERISTICS OF DONOR GRAFTS AND COURSE OF HEMATOPOIETIC RECOVERY.

PATIENT No.	No. OF CD34+ CELLS INFUSED/kg ( $\times 10^{-6}$ )	No. OF CD3+ CELLS INFUSED/kg ( $\times 10^{-5}$ )	DURATION OF NEUTROPENIA*	DURATION OF THROMBOCYTOPENIA†	No. OF TRANSFUSIONS REQUIRED	
					RED CELLS	PLATELETS
			days	days		
1	7.8	1.0	10	0	1	0
2	6.2	1.0	14	11	3	3
3	8.0	1.0	22	11	1	0
4	12.3	1.0	11	0	0	0
5	6.5	1.0	9	0	0	0
6	7.1	1.0	9	8	2	2
7	13.8	1.0	11	0	0	0
8	13.2	1.0	6	0	0	0
9	5.1	1.0	11	6	2	4
10	7.7	1.0	8	0	0	0
Median	7.9	1.0	10	0	1	0
Range	5.1–13.8		6–22	0–11	0–3	0–3

\*Neutropenia was defined as an absolute neutrophil count of less than 500 per cubic millimeter.

†Thrombocytopenia was defined as a platelet count of less than 20,000 per cubic millimeter.

was obtained from all 10 donors. The median dose of CD34+ cells was  $7.9 \times 10^6$  cells per kilogram (range,  $5.1 \times 10^6$  to  $13.8 \times 10^6$ ) (Table 2). Together, the enrichment for CD34+ cells and the depletion of CD3+ cells yielded products in which the mean purity of CD34+ cells was  $84 \pm 11$  percent and in which T cells were reduced by a factor of 30,000 to 100,000. After T cells were added back to the graft, each patient received exactly  $1.0 \times 10^5$  CD3+ cells per kilogram with the graft (Table 2).

#### Hematopoietic Recovery

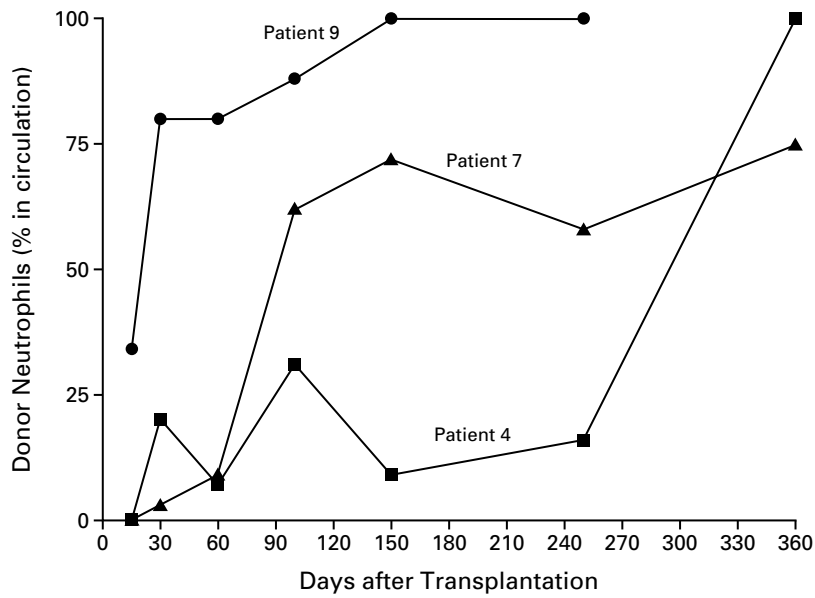
The median follow-up time was 17 months (range, 8 to 26). Hematopoietic recovery was rapid. The median duration of neutropenia (defined as an absolute neutrophil count of  $<500$  per cubic millimeter) was 10 days (range, 6 to 22), and the median duration of thrombocytopenia (defined as a platelet count of  $<20,000$  per cubic millimeter) was 0 days (range, 0 to 11) (Table 2). The blood of most of the patients contained some neutrophils, even at the time of their most severe neutropenia. Only five patients required a brief period of support with transfusions of red cells or platelets after transplantation (Table 2).

#### Donor-Cell Engraftment

Representative patterns of engraftment of donor neutrophils and T cells from 3 patients are shown in Figures 1 and 2, respectively, and the outcomes of transplantation in all 10 patients are given in Table

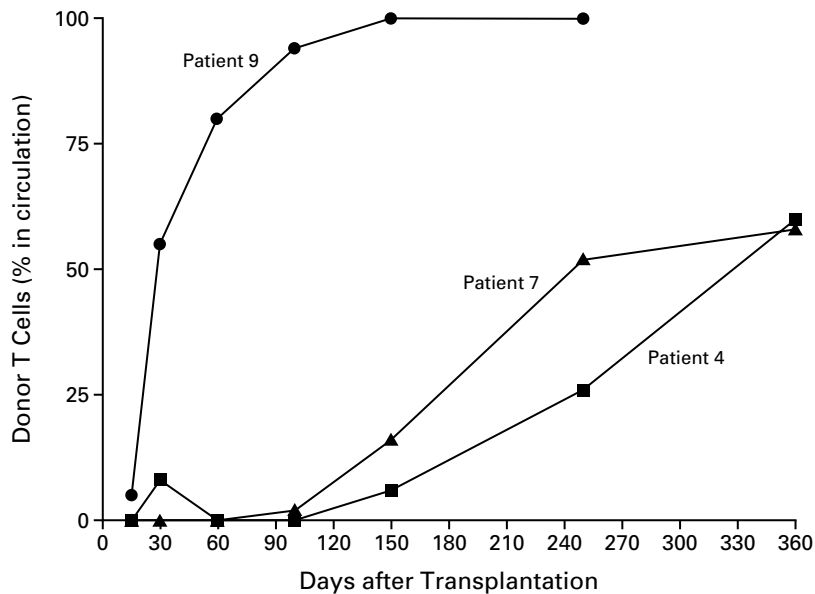
3. In four of the adult patients (Patients 2, 6, 9, and 10), all the myeloid cells in the blood were of donor origin by day 150 after transplantation. In two of the patients who were children (Patients 1 and 4), less than 50 percent of the myeloid cells were of donor origin on day 100, but this proportion progressively increased after cyclosporine treatment was discontinued and repeated infusions of donor lymphocytes were given. Patients 7 and 8 had a mixture of circulating donor and recipient cells for more than 12 months after transplantation. Patient 3, who had antibodies against a broad panel of HLA antigens because allogeneic granulocyte transfusions had been given before the transplantation, never had any evidence of donor stem-cell engraftment. Complete reconstitution of autologous cells occurred, and he recovered to his pretransplantation condition (though he later died, as described below). In Patient 5, who also had limited engraftment of donor myeloid and lymphoid cells, the graft was rejected eight months after the transplantation. At the median follow-up time of 17 months, eight patients had oxidase-positive neutrophils in their blood at levels that could be expected to provide normal host defense (median level, 100 percent donor neutrophils; range, 33 to 100).

With the exception of Patient 3, all the patients received donor-lymphocyte infusions as a means of improving the engraftment of donor stem cells (Table 3). The proportion of circulating donor myeloid cells and T cells increased in all but one (Patient 5)



**Figure 1.** Engraftment of Donor Neutrophils in Three Representative Patients.

In Patient 4, all the neutrophils were of donor origin on day 360, after four infusions of donor lymphocytes. Engraftment was rapid in Patient 9 after a single infusion of donor lymphocytes on day 30. Residual host cells persisted in Patient 7, despite four infusions of donor lymphocytes.



**Figure 2.** Engraftment of Donor T Cells in Three Representative Patients.

The pattern of T-cell engraftment was similar to that of neutrophil engraftment. Residual host T cells persisted in Patient 4 on day 360, despite complete replacement of his neutrophils by those of the donor at that time.

TABLE 3. OUTCOMES AND COMPLICATIONS AFTER TRANSPLANTATION.\*

PATIENT No.	CHIMERISM AT LAST FOLLOW-UP		No. OF LYMPHOCYTE INFUSIONS	GRAFT-VERSUS-HOST DISEASE		OTHER COMPLICATIONS	CLINICAL OUTCOME†
	LYMPHOID	MYELOID		ACUTE	CHRONIC		
	% donor cells‡						
1	95	100	3	—	—	—	Alive and well (26 mo)
2	100	100	1	Grade II	Extensive, involving skin and mouth	Herpes zoster keratitis	Limited chronic graft-versus-host disease (24 mo)
3	0	0	0	—	—	Graft failure§	Death (14 mo)¶
4	75	100	4	Grade I	Limited, involving mouth	—	Alive and well (19 mo)
5	10	0	5	—	—	Graft rejection (8 mo)§	Alive and well (17 mo)
6	100	100	1	Grade II	—	Lymphoproliferative disorder due to Epstein–Barr virus (day 45)	Alive and well (17 mo); graft-versus-host disease resolved
7	52	58	4	—	—	—	Alive and well (17 mo)
8	42	33	5	—	—	Fungal pneumonia (day 4)	Alive and well (16 mo)
9	100	100	1	—	—	Pneumonitis due to fludarabine; fungal pneumonia (day 220)	Death from pneumococcal pneumonia (13 mo)
10	100	100	2	Grade IV	—	—	Death from graft-versus-host disease (8 mo)

\*Dashes denote the absence of the indicated complication.

†The number of months after transplantation is given in parentheses.

‡The presence of oxidase-positive donor myeloid cells was confirmed by flow cytometry.

§Graft failure was followed by autologous hematopoietic reconstitution.

¶Patient 3 died of complications of a second stem-cell transplantation, performed one year after the first transplantation.

of the nine patients who received donor-lymphocyte infusions.

**Clinical Outcome and Adverse Events**

Clinically significant adverse events are listed in Table 3. Patient 9 had interstitial pneumonitis that was attributed to fludarabine and that responded to treatment with corticosteroids.<sup>15,26,27</sup> Cytomegalovirus antigenemia occurred in two patients, but cytomegalovirus disease did not develop in either one.

Prophylactic therapy with interferon gamma and antibiotics was discontinued in all the patients in whom transplantation was successful. Four clinically significant infections occurred in patients in whom normal neutrophils were detected in the circulation. Lymphoproliferative disorder related to Epstein–Barr virus infection was diagnosed in Patient 6 on day 45 after the transplantation; it resolved after the dose of cyclosporine was reduced. Herpes zoster keratitis was diagnosed in Patient 2 while he was being treated for graft-versus-host disease. A fungal pneumonia was diagnosed in Patient 9 on day 220 after the transplantation and resolved after treatment; fatal pneumococcal sepsis then developed in this patient on day 420 after the transplantation. A postmortem exami-

nation revealed multiple granulomas in the lung and liver, bilateral adrenal hemorrhage, and an invasive fungal infection at a site of pulmonary hemorrhage.

In four patients, the granulomas of the lungs, skin, or gastrointestinal tract that were present at the time of transplantation had resolved or improved at the time of the most recent follow-up. No new granulomatous complications occurred during follow-up in any of the recipients in whom transplantation was successful.

One year after the failed attempt at stem-cell transplantation, Patient 3 underwent a second stem-cell transplantation with the use of a radiation-based conditioning regimen on an off-protocol basis. Although engraftment of the donor stem cells was successful, the patient died of complications from hemorrhagic cystitis due to polyomavirus type BK.

**Graft-versus-Host Disease**

Acute graft-versus-host disease (grade II, III, or IV)<sup>28</sup> occurred in three patients, all of whom were adults (Table 3). Patients 2 and 6 had grade II graft-versus-host disease involving the skin after a donor-lymphocyte infusion. In Patient 6 the disease responded to treatment with corticosteroids and cyclosporine;

in Patient 2, chronic graft-versus-host disease of the skin and oral mucosa developed and responded to treatment with thalidomide. In Patient 10, grade IV graft-versus-host disease involving the intestine and the skin developed after complete donor myeloid chimerism was established on day 145. This patient subsequently died of a fungal infection that developed as a result of prolonged therapy for his graft-versus-host disease.

## DISCUSSION

By combining a nonmyeloablative conditioning regimen with transplantation of a T-cell–depleted HLA-identical allograft, we tested a method of allogeneic stem-cell transplantation that emphasized safety but that carried an increased risk of incomplete engraftment of the donor hematopoietic cells or graft rejection. In female carriers of the X-linked form of chronic granulomatous disease, recurrent infections do not develop unless lyonization is skewed such that less than 10 percent of neutrophils are capable of normal oxidase function. Therefore, even partial engraftment of donor stem cells should restore normal immune function in the recipient.<sup>8,9</sup> Longer follow-up of these patients is required to confirm this expectation.

Although the number of patients in this study is small, the absence of transplantation-related death among the children compares favorably with that in other studies of allogeneic stem-cell transplantation for nonmalignant disorders in which myeloablative bone marrow conditioning was used. In a series of 222 children with thalassemia, Lucarelli et al. observed a one-year overall survival of 82 percent; the mortality from graft-versus-host disease was 5 percent.<sup>29</sup> The same investigators reported an estimated survival of 75 percent in a group of adults with thalassemia (and without chronic active hepatitis) who were treated with conventional stem-cell transplantation.<sup>30</sup> In two studies of children with sickle cell anemia, one involving 50 children and one involving 22, the survival rates were 91 percent and 96 percent, respectively.<sup>31,32</sup> Transplantation-related mortality rates in patients with immunodeficiency disorders are higher than those in patients with hemoglobinopathies. Four reports have presented the outcomes of 29 children with the Wiskott–Aldrich syndrome, leukocyte-adhesion deficiency, the Chédiak–Higashi syndrome, or major-histocompatibility-complex class II deficiency who underwent conventional transplantation of stem cells from HLA-identical siblings.<sup>33–36</sup> Transplantation-related mortality in this population of patients was 24 percent, and death from graft-versus-host disease occurred in 10 percent (3 of the 29 patients).

Of the five children in our series, all of whom had at least partial engraftment of donor cells, only one had acute graft-versus-host disease, which was mild (grade I). However, acute graft-versus-host disease developed in three of the four adult patients with en-

graftment. Two had grade II and one had grade IV disease. Although younger age is partially responsible for this difference,<sup>37</sup> the mixed hematopoietic chimerism that existed for more than four months in all the children probably provided added protection against graft-versus-host disease. Although the mechanism of this effect is poorly understood, suppression of graft-versus-host disease has been observed in murine models of mixed hematopoietic chimerism.<sup>38–41</sup> Among patients who had mixed hematopoietic chimerism after allogeneic stem-cell transplantation for aplastic anemia, the incidence of graft-versus-host disease was significantly lower than that among patients with complete engraftment.<sup>42</sup>

Our data confirm observations by other investigators that donor lymphocytes, infused in graded increments, can facilitate engraftment of donor stem cells.<sup>10,20,22</sup> Donor T cells cause immunologic clearance of residual host lymphocytes and stem cells, allowing unhindered engraftment and growth of the donor stem cells.<sup>40,43,44</sup> Andreani et al. used conventional stem-cell transplantation without delayed donor-lymphocyte infusions and observed a graft-rejection rate of 84 percent among patients with thalassemia who had more than 25 percent residual host cells in their circulation two months after the transplantation.<sup>45</sup> Of the seven patients in our study with more than 25 percent circulating host cells at two months, graft rejection occurred in only one.

In a placebo-controlled trial of interferon gamma therapy for chronic granulomatous disease,<sup>1</sup> patients in the placebo group had 55 serious infections during 48 patient-years of follow-up, whereas patients in the interferon gamma group had 20 serious infections during 47 patient-years of follow-up. By contrast, during 13 patient-years of follow-up after discontinuation of interferon gamma therapy, we observed four serious infections after successful engraftment of donor stem cells. All four of these infections were probably a consequence of delayed recovery of T-cell function. In Patient 8, a fungal infection developed before the appearance of donor neutrophils in the blood. Given that patients who enrolled in our study tended to have a severe form of chronic granulomatous disease, the results suggest a clinically significant improvement in myeloid immune function. Furthermore, we observed resolution of granulomatous disease of the skin, lungs, esophagus, and rectum in patients with either mixed or complete donor hematopoietic chimerism.

Despite the reduced toxicity of nonmyeloablative bone marrow conditioning, our approach to stem-cell transplantation in patients with chronic granulomatous disease still carries considerable risks. In Patient 6, because of profound immunosuppression in the early period after transplantation, a lymphoproliferative disorder associated with Epstein–Barr virus infection developed. In Patient 9, despite complete

engraftment with oxidase-positive neutrophils and the absence of graft-versus-host disease, a fungal pulmonary infection developed 7 months after the transplantation, and fatal pneumococcal sepsis occurred 14 months after the transplantation. All of these infections are a reminder that complete immune reconstitution after allogeneic stem-cell transplantation for chronic granulomatous disease may take longer than a year.<sup>46</sup> Although depletion of T cells from the graft is effective in reducing the risk of graft-versus-host disease, chronic or severe acute graft-versus-host disease (as in Patients 2 and 10, respectively) may be a consequence of donor lymphocyte infusions.

Our results suggest that the transplantation of hematopoietic stem cells from an HLA-identical sibling, combined with low-intensity conditioning, reduces conditioning-related morbidity and mortality. In children, depletion of T cells from the allograft seems to result in prolonged mixed hematopoietic chimerism and to reduce the risk of graft-versus-host disease. In adults, this condition remains a serious problem. Patients with chronic granulomatous disease who have an HLA-identical family member and a history of recurrent life-threatening infections should be considered candidates for this procedure before irreversible organ damage or transfusion-related alloimmunization occurs. However, we do not recommend it for patients without an HLA-matched family member.

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