CD8-Depleted Donor Lymphocyte Infusion as Treatment for Relapsed Chronic Myelogenous Leukemia After Allogeneic Bone Marrow Transplantation

By Sergio Giralt, Jeane Hester, Yang Huh, Cheryl Hirsch-Ginsberg, Gabriela Rondón, David Seong, Ming Lee, James Gajewski, Koen Van Besien, Issa Khouri, Rakesh Mehra, Donna Przepiorka, Martin Körbling, Moshe Tai, Hagop Kantarjian, Harald Fischer, Albert Deisseroth, and Richard Champlin

Donor lymphocyte infusions can reinduce complete remission in the majority of patients with chronic myelogenous leukemia (CML) who relapse into chronic phase after allogeneic bone marrow transplantation (BMT). Such infusions are associated with a high incidence of graft-versus-host disease (GVHD) and marrow aplasia. BMT using selective depletion of CD8+ lymphocytes from donor cells reduces the incidence of GVHD without an increase in leukemia relapse. We hypothesized that infusion of CD8-depleted donor peripheral blood lymphocytes could also reinduce complete remissions with a lesser potential to produce symptomatic GVHD in patients with CML who relapsed after allogeneic BMT. Ten patients with Ph(+) CML who relapsed a median of 353 days after BMT (range, 82 to 1,096 days) received donor lymphocyte infusions depleted of CD8+ cells. Nine patients received a single infusion and 1 received two infusions. Four patients were treated while in chronic phase with clonal evolution, 2 during accelerated phase, 3 during blast crisis, and 1 in a cytogenetic relapse. A mean of 0.9 ± 0.3 x 10^6 mononuclear cells/kg were infused, containing 0.6 ± 0.4 x 10^6 CD8+ cells/kg. Six patients achieved hematologic and cytogenetic remission at 4, 8, 11, 15, 39, and 54 weeks after lymphocyte infusion. Two patients developed grade II acute GVHD, and 1 patient developed mild chronic GVHD. We conclude that donor lymphocyte infusions depleted of CD8+ cells can induce remissions with a low rate of severe acute GVHD in patients with CML who relapse after allogeneic BMT, supporting the hypothesis that CD8+ lymphocytes are important effectors of GVHD, but may not be essential for the graft-versus-leukemia effect against this disease. Further controlled studies are required to confirm these preliminary observations.

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Donor Lymphocyte infusions are effective therapy for patients with chronic myelogenous leukaemia (CML) who relapse after an allogeneic bone marrow transplantation (BMT). This procedure has reinstituted cytogenetic and hematologic remission in approximately 80% of patients with a cytogenetic or chronic-phase relapse. However, lymphocyte infusions are frequently associated with adverse effects including graft-versus-host disease (GVHD) in approximately 80% of recipients. Pancytopenia and marrow aplasia has been reported with an incidence ranging from 0% to 100%, although, in the largest series presented, the overall incidence of this complication was approximately 30%. These complications have been the major causes of treatment-related mortality, which has occurred in up to 20% of cases.

In rodents, depletion of the CD8+ cytotoxic/suppressor subset of T lymphocytes is sufficient to reduce or prevent GVHD in some, although not all, H-2-compatible minor antigen-disparate donor-recipient strain combinations. In humans, selective CD8+ T-cell depletion of donor marrow significantly reduced the rate of acute GVHD compared with unmodified marrow in a randomized controlled trial. The risk of relapse was not increased with selective depletion of CD8+ cells in patients with CML consistent with preservation of the graft-versus-leukemia (GVL) effect, at least for this malignancy.

Thus, CD8-depleted transplants appear to have a reduced capacity to produce acute GVHD, yet retain GVL activity. Therefore, we evaluated infusion of donor lymphocytes depleted of CD8+ cells as a treatment for CML that had relapsed after an allogeneic BMT.

PATIENTS AND METHODS

Patient characteristics. Ten patients received infusions of CD8-depleted donor lymphocytes during the period from December 1992 until December 1994. The study was approved by the institutional review board, and patients and donors gave informed written consent according to institutional policy.

Seven patients were women and 3 were men. Patient and donor characteristics are summarized in Tables 1 and 2. The median age of the patients was 38 years (range, 25 to 48 years). Three patients had received their initial transplant while in blast crisis; the other 7 patients were in chronic phase. Seven patients received marrow grafts from matched sibling donors and 3 received unrelated donor transplants. The conditioning regimen included total body irradiation (TBI) in 7 patients and combination chemotherapy using thiota, busulfan, and cyclophosphamide in 3. Prophylaxis for GVHD consisted of T-cell depletion and posttransplantation immunosuppressive therapy in 6 patients and of combination immunosuppressive therapy alone in 4 patients.

The patients had relapsed a median of 353 days after BMT (range, 82 to 1,096 days); 1 relapsed with isolated cytogenetic abnormalities detected by fluorescent in situ hybridization (FISH) for the Philadelphia chromosome (Ph), 4 relapsed into a clinical chronic phase with additional cytogenetic abnormalities (clonal evolution), 1 relapsed into accelerated phase, and 4 were in blast crisis.

Immunosuppressive therapy was discontinued at the time of relapse for all patients. The initial therapy for relapse consisted of hydroxyurea and interferon-α (IFN-α) for 3 patients and of these two agents in combination with interleukin-2 (IL-2) in 5 patients. One patient (unique patient no. [UPN] 92111) received no therapy before donor lymphocyte infusion. Treatment was administered for...
## Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>UPN</th>
<th>Age/Sex</th>
<th>Stage at BMT</th>
<th>GVHD Prophylaxis</th>
<th>Onset of Relapse From BMT (d)</th>
<th>Time to Infusion (d)*</th>
<th>Stage at Infusion</th>
<th>Prior Treatment</th>
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<td>43/M</td>
<td>CP</td>
<td>CSA/MTX</td>
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<td>790</td>
<td>AP</td>
<td>IFN</td>
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<td>FK506/MTX</td>
<td>206</td>
<td>376</td>
<td>AP</td>
<td>High-dose melphalan and allo-PBSCT</td>
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</table>

Abbreviations: Rx, treatment; CP, chronic phase; CPe¢, chronic phase with clonal evolution; BC, blast crisis; CSA, cyclosporine; MTX, methotrexate; XZ, anti-CD6 ricin immunoconjugate (Xomazyme); MP, methylprednisolone; PBSCT, allogeneic peripheral blood stem cell transplantation.

* Time from relapse to donor lymphocyte infusion.
‡ E-rosetting.
§ Target number of mononuclear cells to be collected was 2 to 3 × 10^8/kg of recipient body weight. Donors were single or consecutive apheresis procedures; un-related volunteer donors underwent two consecutive apheresis procedures at another site and cells were transported via courier to M.D. Anderson Cancer Center for processing. The donor for UPN 94002 was collected for a second time 6 months after the initial infusion. These cells were subsequently CD8-depleted and infused at that time. The peripheral blood mononuclear cells were separated on a 60% Percoll gradient according to a previously published technique. The CD8+ cells were depleted by immunomagnetic separation using an anti-CD8 monoclonal mouse antibody according to previously described techniques. In brief, the separated cells were incubated with 10 μg anti-CD8 monoclonal antibody per 10^7 cells for 30 minutes at 4°C. The cells are washed twice and incubated with 10% FCS before apheresis.

## Table 2. Donor Lymphocyte Infusion Characteristics and Outcome

<table>
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<tr>
<th>UPN</th>
<th>Donor Type</th>
<th>Donor Age/Sex</th>
<th>MNC (&gt;10^9/kg)</th>
<th>CD3+ (&gt;10^9/kg)</th>
<th>CD4+ (&gt;10^9/kg)</th>
<th>CD8+ (&gt;10^9/kg)</th>
<th>CD56+ (&gt;10^9/kg)</th>
<th>Post-Rx</th>
<th>GVHD</th>
<th>Response</th>
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<td>42.2</td>
<td>43.5</td>
<td>0.7</td>
<td>9.5</td>
<td>IFN</td>
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<td>Complete</td>
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<tr>
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<td>6.7</td>
<td>IFN</td>
<td>AGVH G/liver</td>
<td>Complete</td>
</tr>
</tbody>
</table>

Abbreviations: SMR, sibling matched related; MUD, matched unrelated donor.

Donor lymphocyte collection and depletion procedure. The lymphocyte donors were the original BM donors in all cases. Eight donors underwent a single leukapheresis at M.D. Anderson Cancer Center using the COBE SPECTRA continuous flow blood cell separator (COBE, Lakewood, CO). One and a half to two times the total blood volume was processed at a collection rate of 1.5 mL per second using acid citrate dextrose (ACD-A) as anticoagulant. The target number of mononuclear cells to be collected was 2 to 3 × 10^8/kg of recipient body weight. Two donors required more than a single apheresis procedure. A unrelated volunteer donor underwent two consecutive apheresis at another site and cells were transported via courier to M.D. Anderson Cancer Center for processing. The donor for UPN 94002 was collected for a second time 6 months after the initial collection. These cells were subsequently CD8-depleted and infused at that time.
Sheep antise- IgG beads (2 bead/cell; Dynabeads M-450; Dynal Inc., Santa Ana, CA) for 30 minutes on a rotator. The cells were then passed through a high magnetic gradient separation column. The adequacy of cell depletion was assessed by flow cytometry. The CD8-depleted donor lymphocytes were infused through a peripheral vein over 10 to 15 minutes.

Nine patients received a single infusion of CD8-depleted donor lymphocytes. One patient (UPN 94002) required 6 U of blood for treatment of hemorrhage during a surgical procedure 3 months after initial infusion. Six months after his initial infusion, he showed no signs of response and underwent a second infusion of CD8-depleted donor lymphocytes.

Flow cytometry. Lymphocyte subsets were analyzed by two-color flow cytometry before and after CD8 depletion to determine the relative and absolute numbers of CD3+, CD3+CD4+, CD3+CD8+, CD3+CD56+, and CD3+ cells. Cells (1 × 10⁷) from each sample were stained with monoclonal antibodies for the specific antigen (Becton Dickinson, San Jose, CA) by a dual-color staining technique. Cells were analyzed on a FACScan (Becton Dickinson, Palo Alto, CA) equipped with a 15-mW argon ion laser connected to a Hewlett Packard 300 computer system (Hewlett Packard, Palo Alto, CA) according to previously described techniques.

Study end points and analysis. Patients were evaluated at least weekly for the first 4 weeks and quarterly thereafter by physical examination, peripheral blood counts, and differential. BM was aspirated 3 and 6 months after CD8-depleted donor lymphocyte infusion and more frequently if clinically indicated.

The response criteria used were those proposed by Talpaz et al. for biologic therapies for CML. Complete hematologic remission was defined as normalization of the peripheral blood count with a WBC < 10.0 × 10⁹/L, a platelet count of less than 450 × 10⁹/L, the absence of peripheral blasts, promyelocytes, or myelocytes, and the disappearance of all signs and symptoms of the disease. Complete cytogenetic response was defined as the absence of Ph(+) metaphases in a sample containing at least 10 metaphases. A partial cytogenetic response was defined as a response with the lowest percentage of Ph(+) metaphases between 1% and 34%. A minor cytogenetic response was defined as a response with the lowest percentage of Ph(+) metaphases between 35% and 90%.

Toxicity was scored according to National Cancer Institute common toxicity criteria. Acute and chronic GVHD were scored according to standard criteria.

Cytogenetic analysis. Chromosome studies on BM cells were performed on all 10 patients before lymphocyte infusion and periodically thereafter using standard techniques. Twenty-five metaphases were analyzed, if possible, and reported according to standard nomenclature.

The patient in isolated cytogenetic relapse was diagnosed using hypermetaphase FISH techniques for the Ph+ cells using previously described techniques. In brief, BM aspirates were placed in culture for 24 hours. Colcemid (1 μg/mL) and cells were cultured for another 24 hours. A probe generated by inter-Alu-polymersase chain reaction (PCR) from the DNA of a hybrid cell containing only 5 Mb of human DNA spanning the breakpoint on chromosome 9q34 was used and 400 to 500 metaphases were analyzed. Cells with three signals were classified as Ph+, whereas cells with two signals were classified as Ph-. Using this technique, no false-positives were observed in 10 normal controls (D. Seong, personal communication, June 1995).

PCR amplification. Amplification of bcr/abl transcripts was performed by PCR, as previously described. In brief, total cellular RNA was prepared from BM and its integrity was determined by ethidium bromide staining. One to ten micrograms of total cellular RNA was reverse-transcribed with Moloney murine leukemia virus reverse transcriptase and antisense oligonucleotide c-abl (−). Two other nucleotides were added for amplification after the reverse transcription reaction was completed, i.e., bcr (+) and abl (+). The reaction was performed in a thermocycler (Perkin-Elmer-Cetus Corp., Norwalk, CT) for 50 cycles. The PCR-amplified products were loaded onto a 3% Nusieve agarose gel and then transferred to a nylon membrane after denaturation. Hybridization of the PCR-amplified products was performed with a mixture of 5'-end radiolabeled probes L-6 and K-28 derived from the sequences at the bcr/abl junction. Autoradiography was performed against an intensifying screen for 48 hours. Two negative controls were run on all samples to control for contamination and all samples were performed in duplicate. The presence of a K-28 message with a 155-bp fragment or a 80-bp L-6 message in an optimally amplified sample was considered to be a positive test result.

Detection of BCR-ABL fusion DNA (Southern blot analysis). DNA was purified from BM aspirate pellets by using a Nucleic Acid Extractor 340A or 341A (Applied Biosystems Inc, Foster City, CA) with standard phenol/chloroform extractions and proteinase K digestion. As previously reported, 10 μg of DNA was digested with Bgl II and Xba I endonucleases (Boehringer Mannheim, Indianapolis, IN). The DNA fragments were separated by size by electrophoresis through a 0.7% agarose gel and subsequently transferred to a nylon filter, in accordance with the manufacturer's instructions (Oncor, Gaithersburg, MD). They were hybridized with the universal bcr probe (TransProbe-1; Oncogene Sciences Inc, Manhasset, NY). After hybridization, the blots were exposed to Kodak X-OMAT AR x-ray film (Eastman Kodak, Rochester, NY) for 3 days at −70°C. The initial assessment of rearrangements was made on this 3-day film, and an additional film was reviewed after 10 to 14 days to check for trace levels of rearrangements that might have been missed on the initial film.

Chimerism studies. Responding patients were assessed at different time points for hematopoietic chimerism using conventional cytogenetic testing, as described above; analysis of restriction fragment length polymorphisms (RFLP) at the AY-29 or YNH24 loci, using a previously described method, and FISH for patients receiving sex-mismatched allografts.

RESULTS

Donor lymphocyte collection and infusion. The mean number of mononuclear cells collected from the donors was 11.08 ± 4.1 × 10⁸. These cells contained 68.2% ± 6.3% CD3+ cells; 52.7% ± 3.9% CD3+CD4+ cells; 22.1% ± 6.3% CD3+CD8+ cells; and 15.4% ± 5.7% CD3+CD56+ cells.

Before CD8 depletion, the lymphocyte preparations contained 67.9 ± 18.2 × 10⁹ CD3+ cells/kg; 52.5 ± 13.7 CD3+CD4+ cells/kg; 21.8 ± 7.1 CD3+CD8+ cells/kg; 15.2 ± 6.0 CD3-CD56+ cells/kg; and 0.2 ± 0.1 CD34+ cells/kg. After CD8 depletion, the mean cell dose infused was 0.9 ± 0.3 × 10⁹ cells/kg containing 47.9 ± 16.2 × 10⁹ CD3+ cells/kg; 46.5 ± 14.7 × 10⁹ CD3+CD4+ cells/kg; 0.6 ± 0.4 × 10⁹ CD3+CD8+ cells/kg; 9.8 ± 4.8 × 10⁹ CD3-CD56+ cells/kg; and 0.2 ± 0.1 × 10⁹ CD34+ cells/kg. Individual cell dose values are stated in Table 2.

Toxicity and response. None of the 10 donors experienced any adverse effects from the lymphocyte collections except the minor discomfort associated with peripheral vein puncture. All recipients tolerated the donor lymphocyte infusion without acute adverse effects.

Six patients have achieved complete hematologic and cytogenetic remissions with CD8-depleted donor lymphocyte infusions. Five patients infused in cytogenetic relapse or...
chronic phase with clonal evolution achieved complete cytogenetic and hematologic remissions at a median of 13 weeks after the initial donor lymphocyte infusion and were in unmaintained remission at 9, 46, 56, 64, and 83 weeks of follow-up. One patient (UPN 93222) infused in accelerated phase achieved a complete hematologic and cytogenetic remission 5 weeks after lymphocyte infusion, but died in remission from sepsis 12 weeks after lymphocyte infusion. The other patient infused during accelerated phase progressed to blast phase 12 weeks after infusion and is being prepared for a second transplant. Three patients infused during blast crisis had progressive disease within 10 days of the lymphocyte infusion and died of their disease.

Three of the five responding patients have become negative for the BCR/ABL transcript as determined by the PCR techniques.

Five of six responding patients had a nadir of neutrophil counts at 31, 55, 64, 206, and 429 days after the initial donor lymphocyte infusion. The neutropenia resolved spontaneously in 1 week in 4 patients (UPN 87002, 90204, 91137, and 93222). Patient UPN 94002 did not respond to the first infusion, but developed severe neutropenia in association with the antileukemic response after the second lymphocyte infusion; neutrophil counts less than 1.0 x 10^9/L lasted 10 weeks despite treatment with G-CSF. Platelet count nadirs of less than 20 x 10^9/L occurred in 4 of the 6 responding patients at 43, 62, 86, and 429 days after donor lymphocyte infusion. Platelets levels remained less than 20 x 10^9/L for 1 to 2 weeks in patients UPN 87002, 90204, and 91137. Patient UPN 94002 has had severe thrombocytopenia lasting 23 weeks and still requires platelet transfusions. Patient UPN 92111 responded without developing severe cytopenia (Table 3, Table 4).

Acute and chronic GVHD. Two patients have developed acute GVHD at 28 and 30 days after lymphocyte infusion. Patient UPN 93222 developed diarrhea and increased bilirubin and alkaline phosphatase. Gastric and liver biopsies showed characteristic features of GVHD. He responded promptly to steroid therapy and had no evidence of GVHD at the time of his death from sepsis 8 weeks later. Patient UPN 92111 developed a skin rash associated with fever and photophobia. Skin biopsy was consistent with GVHD and she responded to systemic steroid therapy without developing visceral involvement.

One patient (UPN 91137) developed lichenoid changes of the oral mucosa consistent with mild chronic GVHD at 4 months after donor lymphocyte infusion and required steroid therapy. No other cases of chronic GVHD have occurred.

Chimerism. All patients had predominantly host-derived hematopoiesis with a minority population of residual donor cells before CD8-depleted donor lymphocyte infusion, as assessed by conventional cytogenetic techniques, RFLP, or FISH for the X and Y chromosome. Chimerism analysis by RFLP or cytogenetics failed to detect residual host hematopoiesis in 5 of the responding patients at the time of complete cytogenetic remission. In patient UPN 87002, FISH for the X and Y chromosomes showed that 591 of 649 cells (91%) were of recipient origin before receiving CD8-depleted donor lymphocyte infusion and that 4 of 413 (0.1%) cells were considered to be residual recipient cells at the time of complete cytogenetic remission. In patient UPN 92111, pretreatment assessment determined that 328 of 400 metaphases were of recipient origin, with 9 of 400 cells being positive for the Ph. Eight weeks after CD8-depleted donor lymphocyte infusion, no Ph^+ metaphases were observed and 295 of 500 metaphases analyzed remained of recipient origin. Twenty weeks after CD8-depleted donor lymphocyte infusions, no Ph^+ metaphases were observed on either conventional cytogenetic analysis or FISH; 301 of 500 cells were recipient sex in origin at this time.

DISCUSSION

Since the original report by Kolb et al' in 1990, numerous studies have confirmed the efficacy of donor lymphocyte infusion in reinducing complete hematologic and cytogenetic remission in patients with CML who relapsed after allogeneic BMT.24 These data represent the most compelling evidence of a GVL effect against this disease.

These reports have usually involved small number of patients with varying cell dosages.15,16 Acute GVHD occurred in 50% to 100% of the responding patients, usually preceding or accompanied by a period of pancytopenia. Mackinnon et al20 recently reported that patients with CML relapsing after a T-cell-depleted allogeneic BMT receiving relatively low T-cell doses (1 x 10^7 to 5 x 10^8 cells/kg) than what has traditionally been reported had a lower incidence of acute GVHD (1 of 11 patients). These data suggest that GVHD may depend on the lymphocyte dose infused, although others have failed to find a
correlation between cell dose and the incidence or severity of GVHD. These conflicting results underscore the fact that the relationship between the cell dose infused and the incidence of GVHD is not known at this time.

Pancytopenia and marrow aplasia occurred in varying degrees, presumably as host leukemic hematopoiesis was inhibited, and before donor-derived hematopoietic cells could regenerate. GVHD and aplasia are the major causes of morbidity and treatment-related mortality associated with donor lymphocyte infusions. In one study, patients treated while in isolated cytogenetic relapse had a higher response rate (7 of 7) than did patients in hematologic relapse (3 of 7), with no instances of marrow aplasia seen in the former group. Patients typically return to complete chimeras with exclusively donor-derived hematopoiesis, suggesting that the GVL process may target host-derived normal as well as leukemic cells. Hematologic recovery depends on the presence of donor-derived hematopoietic progenitors. Thus, the degree of aplasia and pancytopenia that occurs after donor lymphocyte infusions would be expected to be less in patients with early relapse in which hematopoiesis is still predominantly donor-derived.

The cell populations mediating the GVL effect are incompletely defined. We hypothesize that the antileukemic effect of donor lymphocyte infusions is induced by a direct immunologic mechanism mediated through either donor CD4+ cells or natural killer cells that were not eliminated by the depletion procedure. Leukemia-reactive CD4+ and CD8+ cytotoxic T-lymphocyte clones have been identified by various investigators. In one study, the presence of large numbers of antileukemia cytotoxic T-lymphocyte precursor (Lk-CTLP) correlated with leukemia-free survival. Lk-CTLP have also been shown to increase after infusion of unmanipulated donor lymphocytes for CML relapse after allogeneic BMT. Because our patients received a small number of CD8+ lymphocytes, and these cells may have expanded in vivo; we cannot be certain that CD8+ cells are not involved in the GVL effect. Likewise it is possible that the infused CD4+ cells provided help to endogenous donor-derived CD8+ cells in mediating GVL.

Marking studies will be required to track the behavior of the different lymphocyte subpopulations and could be useful in defining their roles in the GVL effect. Similarly, additional studies using highly purified lymphocyte subpopulations would be more definitive. The lymphocyte subset cell doses administered in our study were significantly lower than those reported by others. It is possible that comparably lower doses of unseparated donor lymphocytes could also be as effective with a lesser potential for GVHD.

The antileukemic effect of donor lymphocyte infusions could be mediated, at least in part, by cytokines. Although IFN-α and IL-2 have been shown to have antileukemic effects in vitro and in vivo, it is unlikely that they were responsible for the responses seen in our patients. Nine patients had failed to respond to IFN-α therapy before lymphocyte infusion, and 2 of the responding patients had disease progression while receiving both agents. Other cytokines, such as IFN-γ or tumor necrosis factor, may be implicated.

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<th>Baseline</th>
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<th>Week 16-24</th>
<th>Week 24-32</th>
<th>Week 32-40</th>
<th>Week 40-48</th>
<th>Week 48-56</th>
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<td>3/3</td>
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* Ph' metaphases per total number of metaphases analyzed.
† Values at 13, 21, and 31 weeks after second infusion.
Possible targets for donor lymphocyte recognition include disparate minor histocompatibility antigens between donor and recipient. Polymorphic hematopoietic lineage antigens could be targets; this concept is supported by the isolation of T-cell clones reactive against normal and leukemic host cells.\textsuperscript{29,30} Leukemia-specific antigens have not been documented, but mutant or fusion proteins, such as the bcr/abl fusion protein, or abnormally glycosylated or phosphorylated peptides could serve as potential targets for immune recognition by donor lymphocytes.\textsuperscript{30}

One important characteristic of this phenomenon is the lag time required before a response. In our series, the responding patients required a median of 12 weeks before achieving a complete response. Responses were usually preceded by a period of pancytopenia followed by hematologic recovery with normal diploid cells. This lag time is similar to that of patients who received infusions of unmanipulated donor lymphocytes who achieved remission between 4 and 24 weeks after the initial donor cell infusion. We hypothesize that this interval could be related to expansion of relevant alloreactive cells to a threshold level necessary to produce the antileukemic effect. As the leukemic burden in the marrow decreases, the inhibitory effects on normal donor hematopoietic cells would be expected to decrease, allowing repopulation by donor myeloid cells. Patients with an insufficient reserve of normal donor stem cells often have a period of prolonged pancytopenia and are at risk for infectious complications. This aplasia can be overcome by infusion of donor hematopoietic cells.\textsuperscript{2,3}

Patients in our series with CML in blast crisis did not respond. The lack of response in these patients could have been due either to the rapid progression of the disease, which does not provide sufficient time for the donor lymphocytes to exert their effects, or to an intrinsic resistance of the leukemic clone.

In summary, this preliminary experience indicates that CD8-depleted donor lymphocyte infusions can reinduce remission in patients with relapsed CML after an allogeneic BMT. The rate of acute GVHD was lower than that observed after infusion of unmanipulated donor lymphocytes. Given the preliminary nature of this trial, further studies involving a larger number of patients are needed before definite conclusions can be made regarding the efficacy and GVHD-inducing potential of CD8-depleted donor lymphocyte infusions. Controlled trials will be needed to determine if CD8-depleted donor lymphocyte infusions improve overall treatment outcome. The lower potential of CD8-depleted donor lymphocyte infusions to induce GVHD or other adverse effects suggests a potential role for prophylaxis, as well as treatment of early recurrence of CML after allogeneic BMT.

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CD8-DEPLETED DONOR LYMPHOCYTE INFUSIONS


CD8-depleted donor lymphocyte infusion as treatment for relapsed chronic myelogenous leukemia after allogeneic bone marrow transplantation

S Giralt, J Hester, Y Huh, C Hirsch-Ginsberg, G Rondon, D Seong, M Lee, J Gajewski, K Van Besien and I Khouri