To the Editor:

Allogeneic bone marrow transplantation (BMT) is the only curative therapy for chronic myeloid leukemia (CML), but relapse occurs in approximately 10% of patients transplanted in chronic phase with non-T-cell-depleted marrow. The risk of relapse is substantially greater if T-cell depletion of donor marrow is used as prophylaxis against graft-versus-host disease (GVHD), when relapse rates of 50% or more have been observed. Management of patients in relapse after BMT is difficult: conventional chemotherapy with hydroxyurea or busulfan offers little prospect of prolonging survival, and cytogenetic remissions after α-interferon (IFN) are rare. Second bone marrow transplants carry a high morbidity and mortality. We report here our experience of treating two patients in cytogenetic relapse after allogeneic BMT with infusions of viable donor buffy coat without additional chemotherapy.

Unique patient number (UPN) 197 is a 32-year-old woman who received a T-lymphocyte-depleted BMT in June 1989 from a phenotypically HLA-identical unrelated male donor, while in the accelerated phase of Ph-positive CML. She developed grade II acute skin GVHD, which responded rapidly to oral prednisolone. A routine follow-up marrow 3 months post-BMT showed 19 normal donor metaphases and a solitary 46,XX,Ph-positive metaphase out of 20 examined. Over the subsequent 11 months the proportion of Ph-positive female metaphases in the marrow gradually increased (Table 1). During this period she developed mild chronic oral GVHD, necessitating treatment with prednisolone and cyclosporin A (CSA). In June 1990 immunosuppressive therapy was discontinued. In August 1990, a marrow aspirate showed 21 of 21 46,XX,Ph-positive metaphases, although there was no evidence of hematologic relapse. Karyotypic studies of her peripheral blood lymphocytes suggested the presence of a chimeric lymphoid population (Table 2).

In August 1990 she received two infusions of fresh buffy coat, containing 2.7 x 10^11/kg nucleated cells, collected by leukapheresis from the original marrow donor. She received no prior condition- ing or GVHD prophylaxis. One week after the second infusion she developed grade III acute skin GVHD, which was treated with oral prednisolone and CSA: PUVA therapy was introduced 1 month later because of poor response. Her skin gradually improved over the next few weeks, and in November 1990, 3 months post-buffy coat infusion, a bone marrow aspirate showed 30 of 30 46,XY normal metaphases (Table 1). Repeat studies of her peripheral blood lymphocytes at this stage showed 100% donor cells (Table 2). Leukemia-specific BCR/ABL mRNA was detectable in peripheral blood at this stage using the polymerase chain reaction (PCR) according to the method of Hughes et al.

In December 1990 she developed extensive chronic skin and oral GVHD. There was little response to alternate day steroids and CSA, and she lost considerable weight. Thalidomide was commenced with modest improvement. In May 1991 she remained in complete hematologic and cytogenetic remission. BCR/ABL transcripts were still detectable by PCR in February 1991, but could no longer be detected at time of most recent studies in June and August 1991.

UPN 116, a 39-year-old woman, received a T-cell-depleted allogeneic BMT from her HLA-identical brother in February 1986 while in chronic phase of Ph-positive CML. She developed grade II acute skin GVHD that responded to high-dose steroids. She developed extensive chronic skin GVHD 4 months post-BMT, requiring therapy with steroids and CSA. Immunosuppressive therapy was discontinued in February 1987. Cytogenetic relapse was first noted in March 1989, when 1 of 18 metaphases in the bone

Table 1. Proportion of Ph-Positive Metaphases in Bone Marrow From the Two Patients Before and After Infusion of Donor Buffy Coat

| UPN 197 | 0/20 (0) | 1/15 (7) | 0/15 (0) | 0/10 (0) | 0/10 (0) | 1/18 (6) | 0/18 (0) | 0/20 (0) | 0/30 (0) |
| UPN 116 | 3/30 (10) | 21/21 (100) | 0/30 (0) | 0/30 (0) | 0/30 (0) | 6/35 (17) | 54/80 (67) | 29/35 (83) | 7/13 (54) |

Table 2. Karyotype of Peripheral Blood Lymphocytes From Case One Stimulated by Phytohemagglutinin (PHA) and Pokeweed Mitogen (PWM) Before and After Donor Buffy Coat Infusion

<table>
<thead>
<tr>
<th>Months Post-BMT</th>
<th>PHA Stimulated</th>
<th>PWM Stimulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte infusion</td>
<td>14</td>
<td>12/30 46, XX</td>
</tr>
<tr>
<td></td>
<td>18/30 46, XY</td>
<td>10/21 46, XX, Ph</td>
</tr>
<tr>
<td></td>
<td>10/21, 46, XY</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1/30 46, XX</td>
</tr>
<tr>
<td></td>
<td>20/30 46, XY</td>
<td>2/3 46, XY</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>13/13 46, XY</td>
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marrow was 46,XX,Ph. The proportion of Ph-positive cells increased over the next 18 months (Table 1). Her peripheral blood lymphocytes all had a 46,XY karyotype.

She received a single infusion of fresh buffy coat, containing 1.75 x 10^9/kg nucleated cells, from her brother in November 1990. Because of her previous GVHD, she was given CSA and short-course methotrexate (MTX) as GVHD prophylaxis. She remained well, but 2 months post-infusion her marrow remained substantially Ph-positive (Table 1), and therefore CSA was stopped. A further marrow examination in March 1991 showed eight of eight 46,XY normal metaphases. Shortly after this she developed mild oral and skin GVHD, which responded rapidly to oral steroids. In July 1991 she remained in complete hematologic and cytogenetic remission. PCR studies, performed on peripheral blood, were positive for CML transcripts in February and May 1991, but were negative at time of most recent studies in August 1991.

The remissions attained by these two patients after buffy coat infusions provide further clinical evidence for the existence of a specific graft-versus-leukemia (GVL) effect after allogeneic BMT.\(^1\) It seems likely that an important component of this effect is mediated by donor T lymphocytes.\(^2\) The antileukemic effect of GVHD is well established: GVHD is associated with decreased relapse rates after BMT for CML.\(^3\) Removal of donor T cells reduces the incidence and severity of GVHD, but greatly increases the risk of relapse.\(^4\) However, patients who develop GVHD despite T-cell depletion still have an increased incidence of relapse,\(^5\) as is the case in our two patients. This suggests that T-cell subsets mediating GVL and GVHD may be separable. This is best illustrated by UPN 116, who relapsed despite extensive GVHD after BMT; she reverted to cytogenetic remission following buffy coat infusion, but only developed minimal GVHD.

Infusions of donor buffy coat have previously been used in leukemia therapy. Sullivan et al.\(^6\) gave donor buffy coat to patients with advanced acute leukemia shortly after BMT in an attempt to reduce relapse risk; however, recipients of this therapy showed similar relapse rates to controls, and had more acute GVHD and reduced survival. More recently Kolb et al.\(^7\) has reported three patients in relapse after BMT for CML, treated with IFN and donor leukocyte infusions. All three attained hematologic and cytogenetic remissions: two patients developed GVHD. These cases differ in several respects from our own: the patients were all in hematologic relapse, and had undergone non-T-cell-depleted transplants. None had developed GVHD at time of BMT. All received IFN concurrent with the donor leukocytes. In addition, we have obtained PCR data on both of our patients: although both remained PCR positive during the first 6 months after buffy coat infusion, UPN 197 was PCR negative at 10 and 12 months, and UPN 116 became PCR negative at 9 months. Although the prognostic significance of these findings is uncertain, the pattern of results is similar to that observed after non T-cell-depleted allogeneic BMT,\(^8\) and suggests that the risk of further relapse for these two patients is similarly low. We believe that donor buffy coat infusions merit consideration in patients who relapse after BMT for CML; however, the development of extensive GVHD in one of our patients indicates that this therapy requires further evaluation.

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J.O. CULLIS
Y.Z. JIANG
A.P. SCHWARER
T.P. HUGHES
A.J. BARRETT
J.M. GOLDMAN

Medical Research Council/Leukaemia Research Fund
Leukaemia Unit
Royal Postgraduate Medical School
Hammersmith Hospital
London, UK

REFERENCES


Donor leukocyte infusions for chronic myeloid leukemia in relapse after allogeneic bone marrow transplantation [letter]

JO Cullis, YZ Jiang, AP Schwarer, TP Hughes, AJ Barrett and JM Goldman