Treatment of Relapsed Acute Leukemia after Allogeneic Transplantation: A Single Center Experience

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ABSTRACT
Relapsed acute leukemia after allogeneic transplantation has a poor prognosis and most reports have focused on the role of second transplants in relapsed patients. We report our single-institution experience on the management of relapsed acute leukemia after allogeneic transplantation. We aimed to describe the outcome of relapsed acute leukemia after allogeneic transplantation at our institution and investigate whether maneuvers intended to augment donor T cell allogeneic reactivity were associated with durable graft-versus-leukemia effects. We analyzed 310 patients with acute leukemia who received allogeneic hematopoietic progenitor cell transplants from HLA-matched donors between 1982 and 2005 (229 with acute myelogenous leukemia, 81 with acute lymphoblastic leukemia). Mean post-transplant follow-up was 5 years (range, 0.5-22 years). Factors associated with relapse incidence, therapy for relapse, response to treatment, and post-relapse survival were assessed. One hundred of 310 patients (32%) with acute leukemia who received allogeneic hematopoietic progenitor cell transplants from HLA-matched donors between 1982 and 2005 (229 with acute myelogenous leukemia, 81 with acute lymphoblastic leukemia). Mean post-transplant follow-up was 5 years (range, 0.5-22 years). Factors associated with relapse incidence, therapy for relapse, response to treatment, and post-relapse survival were assessed. One hundred of 310 patients (32%) with acute leukemia who received allogeneic hematopoietic progenitor cell transplants from HLA-matched donors between 1982 and 2005 (229 with acute myelogenous leukemia, 81 with acute lymphoblastic leukemia and 72 of 229 (31%) with acute myelogenous leukemia at a median of 136 days after transplantation. Median post-relapse survival periods were 51 days for the 69 patients who received chemotherapy/supportive care, 84 days for 11 recipients of donor lymphocyte infusions, 303 days for 13 recipients of second transplants, and 442 days for 7 patients treated with interferon-α and granulocyte-macrophage colony-stimulating factor. A multivariable Cox regression analysis indicated that a longer time to relapse after transplantation, peripheral blood as source of stem cells, and initial post-relapse therapy with cytokines, donor lymphocyte infusions, or second transplants were associated with improved post-relapse survival (P <.001, <.001, and .025). The outlook for patients with post-transplant relapse of acute leukemia is extremely poor; currently, no single therapy consistently results in durable remissions. Our study highlights the need for clinical trials in this area. Therapy with granulocyte-macrophage colony stimulating factor and interferon-α-2b is promising and will be pursued in a prospective trial at our center.

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KEY WORDS
Relapsed acute leukemia ● Graft versus leukemia ● Immune therapy

INTRODUCTION
Bone marrow or blood hematopoietic progenitor cell transplantation (HPCT) remains the only potentially curative therapy for patients with high-risk leukemia; but relapse remains a significant problem and is the major cause of post-transplantation mortality. Patients with relapsed leukemia after HPCT have a very poor prognosis and the optimal salvage therapy remains an open question. The existence of a graft-versus-leukemia (GVL) effect in the setting of clinical allogeneic transplantation has been demonstrated for patients with acute leukemia [1], and harnessing this effect in the post-transplantation relapse setting may improve post-relapse outcomes. Although donor lymphocyte infusion (DLI) yields complete remissions in 60%-86% of patients with chronic myelogenous leukemia (CML) relapsed after bone marrow transplantation [2-6], the benefit of DLI for relapsed acute leukemia is limited, with overall survival rates of 15%-20% reported at 1 month to 3 years [4,7-9]. Second transplants are often considered to be the standard of care for patients with relapsed acute leukemia after allogeneic transplantation and can provide du-
rable remissions in the small number of patients who are eligible to receive second transplants. In a report to the International Bone Marrow Transplant Registry (IB-MTR), Eapen et al [10] reported overall survivals of 41% at 1 year and 28% at 5 years after second transplantation for treatment of relapsed acute and chronic leukemia; and Meshinschi et al [11] reported a 56% 1-year survival for 25 pediatric patients who received second transplants for relapsed acute myelogenous leukemia (AML). Of note, younger patients and those with longer remission intervals had improved outcomes. In contrast, Radich et al [12] reported a relapse rate of 76% and a disease-free survival rate of only 10% at 4 years for patients with relapsed AML treated with second transplants [12]. Second transplants are limited by availability of a donor, and comorbidities related to the first conditioning regimen may preclude administration of another course of high-dose cytotoxic therapy. For patients who cannot tolerate further cytotoxic chemotherapy or second transplants, immune therapy aimed at inducing a GVL effect is a feasible option. Immuno-/haplotherapy with interferon-α alone [13,14] or with DLI [6] can effect remissions in patients with CML, but the role of cytokines in the management of AML and acute lymphoblastic leukemia (ALL) relapsing after allogeneic transplantation is poorly defined and limited to case reports [15-20] and small case series [21-24]. To describe the management of relapsed acute leukemia after allogeneic transplantation and the frequency of using different strategies to manage relapse at our institution, we performed a retrospective, single-institution study of patients with acute leukemia who received bone marrow or blood HPCT from HLA-matched donors. We identified the patients who relapsed after transplantation and enumerated the different salvage strategies applied and the clinical outcomes of those relapsed patients. Our goals were to describe the overall incidence of relapse in our cohort, compare outcomes for patients with ALL versus AML relapsed after transplantation, and compare outcomes for relapsed patients treated with salvage chemotherapy versus treatments intended to induce an immune-mediated GVL effect. A secondary objective was to delineate any factors that may have affected the incidence of relapse in our cohort of patients. We present long-term follow-up data on the largest single-institution series of patients with relapsed/refractory AML or ALL after allogeneic HPCT reported to date and demonstrate the feasibility of inducing GVL effects in these patients.

METHODS

Patients and Data Collection

We reviewed 310 consecutive patients who underwent transplantation for acute leukemia at Emory University between 1982 and February 2005. Data regarding patient characteristics, source of stem cells (bone marrow versus blood HPCT), type of transplant donor, disease status at diagnosis, cytogenetics at diagnosis, conditioning regimen, graft-versus-host disease (GVHD) prophylaxis, acute and chronic GVHD, diagnosis of post-transplantation relapse, and type of initial salvage therapy were gathered after institutional review board approval of this retrospective analysis. All grafts were 5/6 or 6/6 HLA-antigen matched from related or unrelated donors. Recipients of cord blood and haploidentical transplants from related donors were not included in this study.

Definitions

Cytogenetic abnormalities were defined as favorable, unfavorable, poor, and unknown risk according to the Southwest Oncology Group classification for AML [25,26] and as unfavorable or favorable for ALL according to previous reports [25,27]. Relapse was defined as the post-transplantation presence of leukemia cells detected by morphology or flow cytometry after a complete remission (CR) had been achieved. Persistent disease was defined as post-transplantation detection of leukemia without documentation of a post-transplantation CR. For acute promyelocytic leukemia or Philadelphia chromosome-positive ALL, the presence of the clonotypic molecular or cytogenetic abnormality was sufficient to diagnose relapsed or refractory leukemia. Response to post-relapse salvage therapy and post-relapse survival were evaluated for each salvage modality, with CRs being hematologic, morphologic, or flow cytometric clearance of leukemic blasts from the blood or bone marrow. Post-relapse survival was measured from the time of relapse to time of death or censored at last contact date if survival status was not known.

Post-relapse Interventions

After the diagnosis of relapse was made, immunosuppression was discontinued in all patients, in the absence of significant GVHD, and salvage therapy was administered as deemed appropriate by the treating physician. For patients whose leukemia relapsed after immunosuppression had been previously discontinued, salvage therapy was given without delay. Types of salvage therapies administered for treatment of relapsed disease were as follows: cytotoxic chemotherapy directed against leukemia cells; second transplants that consisted of administration of a graft containing ≥3 million CD34+ cells from the original donor or from an unrelated donor after full myeloablative or nonmyeloablative conditioning; DLI, which was defined as infusion of a dose of CD3+ lymphocytes (range, 200 000 to 100 million/kg) containing <3 million CD34+ cells/kg with or without prior administration of reinduction chemotherapy; and cytokine therapy, which consisted of treatment with interferon-α.
(3 million units subcutaneously 1-3 times per week) with or without concomitant granulocyte-macrophage colony-stimulating factor (GM-CSF; 500 µg subcutaneously 1-3 times per week). Cytokine treatment was continued until toxicities or signs of GVHD developed or patients progressed. Chemotherapy/other salvage therapy included reinduction with regimens containing any or a combination of cytarabine, anthracycline, etoposide, or vincristine. Other drug therapies including Gleevec for Philadelphia-chromosome positive ALL (n = 1), all-trans retinoic acid or arsenic trioxide for acute promyelocytic leukemia (n = 1) were included in the chemotherapy group.

Statistical Analysis

Kaplan-Meier estimates of overall post-transplantation survival and survival after post-transplantation relapse were calculated for patients with a diagnosis of acute leukemia who underwent allogeneic HPCT. Log-rank statistics were used to compare survival curves. Univariate analyses were performed using logistic regression models. Variables deemed significant on univariate analysis were entered into Cox proportional hazard models for multivariable analysis. Data were entered into the model using a forward conditional method. Two-tailed P values ≤0.05 were considered statistically significant in all analyses. SPSS software (SPSS Inc, Chicago, Ill) was used for all analyses.

RESULTS

The characteristics of 310 patients with ALL (81 patients, 26%) and AML (229 patients, 74%) who received allogeneic transplants are listed in Table 1. Men comprised 54% of the population (168 of 310) and the median age of all patients was 36 years; 32% of patients underwent transplantation with active relapsed or refractory leukemia, and 68% of patients underwent transplantation in CR. The conditioning regimens consisted of cyclophosphamide plus total body irradiation or cyclophosphamide and busulfan for fully myeloablative conditioning (93%) and fludarabine-based reduced intensity conditioning (7%). Complete data regarding incidence and grade/stage of GVHD were not available for the entire 310-patient cohort, but limited data that included the presence or absence of GVHD were available for the 100 patients with relapsed/refractory disease.

Baseline characteristics of the relapsed and nonrelapsed groups were similar, with the exception of disease status at transplantation, donor type, and cytogenetics at diagnosis.

Relapse after Allogeneic Transplantation

In total, 72 of 229 patients (31%) with AML and 28 of 81 (35%) with ALL relapsed at a median of 136 days after transplantation. Cumulative incidences of relapse were 26% for 211 patients who underwent transplantation in CR and 45% for 99 patients who underwent transplantation with relapsed/refractory disease (Figure 1). Characteristics associated with a higher likelihood of post-transplantation relapse on univariate analysis were: active disease at time of transplantation and unfavorable cytogenetics at diagnosis of acute leukemia (P < .001 and .002, respectively). Transplant procured from an unrelated donor was associated with decreased risk of relapse (P = .019). All 3 risk factors remained significantly associated with relapse on multivariable analysis (P < .001, .012, and .017 respectively). When AML and ALL cases were analyzed separately, poor cytogenetic risk was associated with higher risk of relapse among AML cases only (multivariable P = .012), and unrelated donor grafts were associated with decreased risk of

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n = 310)</th>
<th>Relapsed Patients (n = 100)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>81 (26%)</td>
<td>28 (28%)</td>
<td>NS</td>
</tr>
<tr>
<td>AML</td>
<td>229 (74%)</td>
<td>72 (72%)</td>
<td>NS</td>
</tr>
<tr>
<td>Median age</td>
<td>36 (13-68)</td>
<td>35 (15-60)</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>168 (54%)</td>
<td>57 (57%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cyto genetic risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>49 (16%)</td>
<td>14 (14%)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>87 (28%)</td>
<td>21 (21%)</td>
<td></td>
</tr>
<tr>
<td>Unfavorable</td>
<td>90 (29%)</td>
<td>42 (42%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>84 (27%)</td>
<td>23 (23%)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Table 1. Patient Characteristics

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BMT, bone marrow transplantation; HPCT, hematopoietic progenitor cell transplantation; Cy, cyclophosphamide; GVHD, graft-versus-host disease; RIC, reduced intensity conditioning; CSP, cyclosporine with or without methotrexate; TBI, total body irradiation; Cy, cyclophosphamide; CSP, cyclosporine with or without methotrexate; other, T depletion/steroids/t unknown.

*Relapsed versus nonrelapsed patients.
†Information not available for 2 patients.
relapse for ALL cases only \((P = .033)\). Status of leukemia at transplantation maintained its significant association with relapse for patients with AML and with ALL \((P < .001\) for both). Factors not significantly associated with post-transplantation relapse included age at transplantation, diagnosis (ALL versus AML), conditioning regimen, and source of stem cells (peripheral blood versus bone marrow).

**Salvage Modalities to Treat Relapse**

A summary of the various initial therapeutic maneuvers employed after the diagnosis of relapsed or persistent leukemia after allogeneic transplantation is presented in Table 2. Immunosuppressive drug therapy was stopped in all patients upon the diagnosis of relapse, before receiving any other therapy. Twenty-six patients received chemotherapy, radiation to extramedullary sites, antibody therapy, or tyrosine kinase inhibitor as initial treatment of relapse, whereas 43 patients received supportive care without chemotherapy. Thirteen patients, who relapsed at a median of 750 days after transplantation, received second transplants, 12 from the same donor and 1 from a second, matched unrelated donor. Eleven patients, who relapsed at a median of 89 days after transplantation, received DLI containing a median of \(5 \times 10^7\) donor T cells/kg; 4 of 11 patients received DLI containing \(1 \times 10^8\) CD3+ cells/kg after induction chemotherapy according to the schema developed by Collins et al\[28\], and 7 of 11 patients received DLI without preceding chemotherapy. Seven patients, who relapsed at a median of 103 days after transplantation, received GM-CSF/interferon-\(\alpha\) as the first salvage therapy. Second transplants were offered based on donor availability; other therapies were administered based on physician preference. New-onset GVHD developed in 33 patients with relapsed acute leukemia and was more prevalent among recipients of second transplants (7 of 13 patients), DLI (5 of 11 patients), or cytokines (5 of 7 patients). Sixteen of the 69 patients treated with chemotherapy/supportive care developed GVHD after relapse. Development of GVHD after relapse was often, but not always, associated with a GVL effect. This effect was more evident among recipients of cytokines and second transplants, where all patients who developed de novo GVHD had objective responses compared with only 2 responses among patients without post-relapse GVHD \((P < .01)\). Interestingly, among patients with ALL, those who developed de novo GVHD after relapse lived longer than those who did not develop de novo GVHD (median survival, 6 versus 2 months, respectively, \(P = .013\)), but the same association was not observed among patients with relapsed AML \((P = .24)\).

**Survival**

*Post-transplantation survival.* The Kaplan-Meier estimate for 3-year survival for all 310 patients was 32%. Factors significantly associated with shorter post-transplantation survival after transplantation based on univariate analyses included active disease at time of transplantation, unfavorable cytogenetic risk group for patients with AML, older age, and bone marrow as source of stem cells \((P < .001, .001, .045,\) and \( .09\) respectively), with all 3 factors remaining significant on multivariable analysis \((P < .001, .045, .004,\) and \( .016,\) respectively). Kaplan-Meier estimates of survival at 3 years were 43% for 145 patients who underwent transplantation in first CR, 24% for 65 patients who underwent transplantation in second or third CR, and 15% for 99 patients who underwent transplantation with relapsed/refractory disease.

*Survival after post-transplantation relapse.* Median survival for the 100 patients with acute leukemia who relapsed after allogeneic bone marrow or blood HPCT was 65 days. Median post-relapse survivals

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**Table 2. Initial Salvage Therapy for Relapsed Acute Leukemia**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>CR</th>
<th>GVHD after Relapse</th>
<th>Post-relapse Survival (d), Median (Range)</th>
<th>Patients Alive (Days after Relapse for Each Patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo/supportive care (n = 69)</td>
<td>5%</td>
<td>5%</td>
<td>51 (0-1556)</td>
<td>3 (1556, 963, 832)</td>
</tr>
<tr>
<td>Second transplant (n = 13)</td>
<td>8%</td>
<td>7%</td>
<td>303 (40-3695)</td>
<td>1 (3695)</td>
</tr>
<tr>
<td>DLI ± chemotherapy (n = 11)</td>
<td>4%</td>
<td>4%</td>
<td>84 (15-882)</td>
<td>0</td>
</tr>
<tr>
<td>Cytokines (GM-CSF/IFN-(\alpha)) (n = 7)</td>
<td>5%</td>
<td>5%</td>
<td>442 (149-1272)</td>
<td>3 (400, 1247, 1272)</td>
</tr>
</tbody>
</table>

CR indicates complete remission; GVHD, graft-versus-host disease; DLI, donor lymphocyte infusion; GM-CSF/IFN-\(\alpha\), granulocyte-macrophage colony stimulating factor/interferon-\(\alpha\).
were 303 days for the 13 patients who received second transplants, 442 days for the 7 patients who received GM-CSF/interferon-α, 84 days for the 11 patients treated with DLI, 240 days for the 4 patients who received reinduction chemotherapy followed by DLI [28], and 51 days for the 69 patients who received chemotherapy/antibody therapy/radiation or supportive care. Despite the dismal outcome for our cohort of patients with post-transplantation relapse of acute leukemia, we observed that patients who received salvage therapy with second transplants, DLI, or cytokines after withdrawal of immunosuppression lived longer than did patients who were treated with chemo/supportive care alone after withdrawal of immunosuppression (Figure 2). Post-relapse survival was similar for patients with AML and those with ALL (Figure 3). Among the 100 patients with post-transplant relapsed/refractory leukemia, only 7 patients remain alive and 1 has an unknown status. Of the 7 cytokine-treated patients, 3 are alive, 1 without evidence of disease on no immunosuppressive drugs 3.5 years after relapse, another is in CR with chronic extensive GVHD 1 year after relapsing, and the other patient has received intermittent cytokine therapy for persistent disease 3.5 years after initial relapse. Of the 13 patients who received second transplants, 1 remains alive 10 years after relapse. Among the 11 patients who received DLI to treat relapse, there are no long-term survivors. Among the 69 patients who received chemotherapy or supportive care for relapse, 3 remain alive, 1 at 2.3 years after receiving all-trans retinoic acid (ATRA) followed by arsenic trioxide for relapsed acute promyelocytic leukemia, 1 at 4.3 years after receiving imatinib mesylate for relapsed Philadelphia chromosome-positive ALL, and the other patient achieved a CR after withdrawal of immunosuppression alone and has survived 2.7 years after relapse.

**Causes of Death for Patients Relapsing after Allogeneic Transplantation**

The main cause of death for the group of patients with relapsed acute leukemia was leukemia in 74 (80%), followed by infection/other causes in 15 (16%). GVHD was the main cause of death in 4 patients (4%); 3 of those patients had received second transplant or DLI as salvage therapy. Of note, 1 of the patients treated with cytokines died of sepsis during steroid therapy for chronic extensive GVHD.

**Factors Associated with Survival after Post-transplantation Relapse**

Univariate analysis showed that a longer interval between first transplantation and post-transplantation relapse, use of any immune-based therapy (excluding chemotherapy alone and withdrawal of immunosuppression alone), peripheral blood as source of stem cells, and favorable cytogenetic risk group were associated with improved survival after relapse; and multivariable analysis showed that longer time to post-transplantation relapse, peripheral blood as source of stem cells, and immune-based salvage therapies (second transplants, DLI, cytokines) appeared to be associated with improved post-relapse survival (Table 3). The following factors did not significantly influence survival in the setting of post-transplantation relapse: patient age, gender, donor type, or disease type (data not shown).

**DISCUSSION**

Relapse of acute leukemia after allogeneic transplantation remains a significant therapeutic challenge.
and is the main cause of treatment failure after allogeneic transplantation. We have analyzed long-term follow-up data on patients who underwent transplantation at a single institution to evaluate the incidence of relapse in a consecutive series of patients treated at a single institution and to describe the strategies used for treatment of post-transplantation relapse of acute leukemia at our institution. The overall incidence of 32% relapse in our cohort is consistent with the published 30%-60% incidence of relapse of acute leukemia after allogeneic transplantation [29]. As expected, a higher incidence of relapse was observed among patients who underwent transplantation with active leukemia (45%) versus patients who underwent transplantation in CR (26%, Figure 1). This is consistent with reported relapse rates of 45%-51% for patients who undergo transplantation with active disease [30-32]. Lower rates of relapse were seen among recipients of bone marrow or blood HPC transplants obtained from HLA-matched unrelated donors compared with sibling donors, suggestive of an increased GVL effect associated with this donor cell source [33,34]. However, this benefit in relapse was not offset by improved survival for recipients of unrelated donor transplants, likely owing to higher treatment-related mortality. Favorable cytogenetics were associated with lower rates of relapse and improved survival after post-transplantation relapse [26,35].

Our study emphasizes the grim prognosis for patients with relapsed acute leukemia after allogeneic transplantation and highlights the need for more effective therapies. The nature of this nonrandomized, retrospective analysis precludes any definitive conclusion regarding the efficacy or applicability of any particular treatment for leukemia relapsed after allogeneic transplantation, but our observations suggest that therapies aimed at enhancing the GVL effect of allogeneic transplantation, including second transplants, GM-CSF/interferon-α, or DLI may be beneficial for improving post-relapse survival. The use of chemotherapy alone to treat post-transplantation relapse of acute leukemia appears to be largely ineffective. Second transplants, which are often recommended as the standard of care for post-transplantation relapse of acute leukemia, were administered to only a minority of relapsed patients in our cohort (13 of 100 patients), and long-term (5-year) survival after second transplants was only 11%. Historically, only 6%-20% of relapsed patients actually receive second transplants [10,36]. The use of reduced intensity conditioning regimens before second transplants may expand the applicability of second transplants in the relapse setting, but long-term follow-up is limited [36,38-41].

The duration of remission after transplantation was an important determinant of post-relapse outcome, as has been shown in other series [10,37]. Despite the ability of DLI to induce GVL effects in patients with relapsed CML [6,42], the ability of DLI to produce durable remissions for relapsed acute leukemia was not demonstrated in our cohort. We observed an incidence of CR of 45% in 11 patients who received DLI. However those remissions were short-lived and there were no long-term survivors. Other investigators have reported similar results [28]. Collins et al [43] reported fewer responses to DLI for relapsed ALL and postulated that ALL may be less responsive to the GVL effect. This lack of a GVL effect in ALL is supported by the results of a review of 135 leukemic patients who received DLI for treatment of post-transplantation relapse at 27 centers in the European Group for Blood and Marrow Transplantation, where no response to DLI alone was seen among 12 patients with ALL and a modest response of 29% in 17 patients with AML without durable remissions or long-term survival [4]. The addition of cytokine therapy to DLI may increase responses, but may also increase the incidence of life-threatening GVHD [24,44].

The use of interferon-α/GM-CSF to induce a graft versus leukemia effect may be promising as a treatment strategy for patients with acute leukemia relapsed after allogeneic transplantation. Administration of these cytokines produced complete remissions in 5 of 7 (71%) treated patients, including 3 of 4 patients with relapsed AML and 2 of 3 patients with relapsed ALL. Other investigators have also reported on the feasibility of combining these 2 cytokines to treat leukemia [45]. The mechanisms by which these cytokines effect an antileukemia effect are not fully understood, but hypotheses include (1) activation of donor-derived dendritic cells that indirectly present alloantigen and activate donor T cells; (2) differentiation of residual host-type leukemic blasts into cells

### Table 3. Factors Associated with Death after Post-transplantation Relapse

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate</th>
<th>Multivariable</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to relapse &gt;136 d</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>0.35 (0.22-0.57)</td>
</tr>
<tr>
<td>Immune-based salvage therapy</td>
<td>&lt;.001</td>
<td>.025</td>
<td>0.63 (0.38-0.98)</td>
</tr>
<tr>
<td>Peripheral blood as stem cell source</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>0.38 (0.24-0.61)</td>
</tr>
<tr>
<td>Favorable cytogenetic risk group</td>
<td>.040</td>
<td>NS</td>
<td>—</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.

*Odds ratios <1 were associated with longer post-transplantation survival.
with dendritic cell properties that directly present alloantigen and tumor-associated antigens to activate donor T cells; and (3) direct or indirect activation of donor T cells with or without natural killer cells [46-48]. Although the ability of donor dendritic cells to inhibit or augment alloreactivity of donor T cells has been shown in preclinical models [49] and in clinical bone marrow transplantation [50], the ability of exogenously administered cytokines to cause differentiation of leukemic blasts into antigen-presenting cells that activate cytotoxic donor T cells is a hypothesis that should be tested in a prospective clinical trial.

Our study demonstrates the poor outcome of relapsed acute leukemia after allogeneic transplantation and underlines the need for prospective studies of therapies aimed at inducing durable GVL effects.

REFERENCES


