The Role of Disease Stage in the Response to Donor Lymphocyte Infusions as Treatment for Leukemic Relapse

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ABSTRACT
Between 1991 and 1999, 44 leukemic patients received donor lymphocyte infusions (DLIs) at our center (22 patients with chronic myelogenous leukemia [CML]; 10 with acute myelogenous leukemia; 11 with acute lymphatic leukemia; and 1 with myelodysplastic syndrome). Seventeen patients received graft-versus-host disease (GVHD) prophylaxis with methotrexate (MTX) at the time of DLI. In CML patients, 15 of 22 (68%) re-entered complete remission after DLI. At 3 years post-DLI, patients with cytogenetic (n = 10) or molecular (n = 3) relapse had a current leukemia-free survival (cLFS) rate of 85% compared with 0% for patients with hematologic relapse (P < .001). Among 15 CML patients who initially responded to DLI, 4 patients relapsed within the first 2 years. Four of 16 patients (25%) with acute leukemia had an initial response with complete remission after DLI. Two of them subsequently relapsed within 1 year. Patients with acute leukemia who relapsed within 1 year of hematopoietic stem cell transplantation (n = 9) had 0% cLFS at 18 months; patients with later relapse had 29% cLFS (P = .015). The overall probability of cLFS at 3 years for CML patients was 46%. For other diseases, cLFS was 13% at 18 months after DLI. Patients who developed chronic GVHD secondary to DLI showed a 3-year cLFS of 51% compared with 18% for patients without chronic GVHD (P = .022). This study emphasizes the importance of early disease stage and presence of chronic GVHD for effective DLI.

KEY WORDS
Donor leukocyte infusion • Graft-versus-leukemia reaction • Relapse

INTRODUCTION
Allogeneic hematopoietic stem cell transplantation (HSCT) can offer a cure for patients with hematologic malignancies. Although methods are constantly improving, relapsed disease remains a major limitation to long-term patient survival. Different strategies have been explored to address this problem. Increased cytotoxic conditioning regimens have been evaluated but have not been successful in lowering relapse rates, mainly because of increased toxicity [1,2]. A second allogeneic transplantation for recurrent disease has cured only a small number of patients and is also associated with extensive morbidity and mortality [3-6]. It has become evident that patients who develop graft-versus-host disease (GVHD) run a lower risk of recurrent disease than patients without GVHD. This so-called graft-versus-leukemia (GVL) effect was first described in humans by Weiden et al. in 1979 [7] and has been shown to be crucial for long-term remissions, particularly in patients with advanced leukemias [8-12]. Both GVHD and GVL are thought to be mediated by alloreactive donor leukocytes (T cells and natural killer [NK] cells) recognizing host histocompatibility antigens. This supposition has led to the testing of donor buffy coat infusions to augment GVL activity of bone marrow allografts [13] and subsequently to the use of donor lymphocyte infusions (DLIs) as a treatment for leukemic relapse after HSCT [14-17].

The best response to DLI is seen in patients with relapsed chronic myelogenous leukemia (CML), in whom complete remissions (CRs) have been reported in 60% to 80% of these treated patients [16,18-20]. For patients with acute leukemia, the results are less encouraging, with an initial response rate between 10% and 20% [16,18,19]. The
success of DLI in inducing remission is highly correlated to the incidence of acute and chronic GVHD [18], but the mediators of the GVL effect have been difficult to isolate from those causing GVHD. Severe acute GVHD (grades II to IV) subsequent to DLI is common, with incidences varying between 40% and 55% [16,18,20]. Other adverse effects, such as pancytopenia, have been reported in almost 20% of patients [18]. These effects contribute to the toxicity of DLI, resulting in a treatment-related mortality of up to 20% [20].

A thorough understanding of the effects and the kinetics of DLI treatment is essential to optimize treatment protocols. Because many of the previous follow-ups on DLI treatment were based on data from multiple centers with varying, nonstandardized treatment strategies, we wanted to evaluate the outcome at our own center. Therefore, we performed a retrospective analysis of all DLI-treated patients with leukemia or myelodysplastic syndrome (MDS).

**MATERIALS AND METHODS**

**Patients and Donors**

This study includes 44 patients (22 with CML, 10 with acute myelogenous leukemia [AML], 11 with acute lymphatic leukemia [ALL], and 1 with MDS) who received transplants between 1986 and 1999. They all received DLI treatment between 1991 and 1999. Thirty patients were given conventional bulk doses of donor lymphocytes containing variable numbers of CD3+ T cells (bulk dose regimen [BDR]). The remaining patients (n = 14) received escalating doses of lymphocytes containing predefined numbers of CD3+ cells (escalating dose regimen [EDR]). For the majority of patients (n = 38), DLI was given as treatment for recurrent disease, but some patients in the EDR group (n = 6) received DLI prophylactically, to prevent relapse. The patients treated with a prophylactic regimen were included in the study for the evaluation of side effects of DLI. Main patient and donor characteristics are depicted in Table 1. Details regarding conditioning protocols and immunosuppressive regimens have been described in detail [21-23]. The study was granted permission by the local ethics committee. Oral consent was obtained from the patients.

**Definition of Relapse**

Patients who relapse after HSCT do so in a sequential manner, with relapse recognizable first at the molecular level, then at the cytogenetic level, and finally with hematologic evidence of leukemia. For CML patients, a molecular relapse was defined as evidence of recurrent disease only by reverse transcription–polymerase chain reaction (RT-PCR) for *bcr/abl* messenger RNA (mRNA). All patients (CML and non-CML) who had reappearance of a disease-specific chromosome abnormality by fluorescence in situ hybridization or conventional cytogenetics but no morphological signs of disease were defined as cytogenetic relapses. Relapse with detectable disease in blood or bone marrow by morphological analyses was defined as hematologic.

**Definition of Response**

Hematologic remission was achieved if a patient with previous hematologic relapse attained normal blood counts and normalized bone marrow morphology. A patient was considered to have achieved a cytogenetic remission if no disease-specific chromosome abnormality was detectable in the marrow upon cytogenetic analysis. Patients with CML were considered to have achieved a molecular remission when *bcr/abl* transcripts no longer could be detected by RT-PCR.

### Table 1. Pretreatment Characteristics of Patients and Donors*

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>BDR†</th>
<th>EDR‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>44</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td><strong>Patient age, y</strong></td>
<td>30 (3-58)</td>
<td>33 (4-58)</td>
<td>25 (3-53)</td>
</tr>
<tr>
<td><strong>Donor age, y</strong></td>
<td>35 (2-61)</td>
<td>35 (2-60)</td>
<td>29 (2-61)</td>
</tr>
<tr>
<td><strong>Patient sex, M/F</strong></td>
<td>28/16</td>
<td>20/10</td>
<td>8/6</td>
</tr>
<tr>
<td><strong>Donor sex, M/F</strong></td>
<td>30/14</td>
<td>19/11</td>
<td>11/3</td>
</tr>
</tbody>
</table>

- **Diagnosis**
  - AML
  - ALL
  - CR1§
  - >CR1
  - CML
  - CP1
  - >CP1
  - Cytogenetic relapse
  - Molecular relapse
  - Hematologic relapse
  - MDS
  - HLA-matched donor
  -Sibling
  - Parent
  - Unrelated
  - Related donor, 1 antigen mismatched
  - Unrelated donor, 1 antigen mismatched

- **Conditioning regimen**
  - CY + TBI
  - BU + CY
  - T cell-depleted HSCT
  - GVHD after HSCT
  - Grade I
  - Grade II
  - Grade III

- **Cell dose**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>BDR†</th>
<th>EDR‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>—</td>
<td>2.7 (0.1-32)</td>
<td>0.2 (0.02-3.1)</td>
</tr>
</tbody>
</table>

- Data are n or median (range). BDR indicates bulk dose regimen; EDR, escalating dose regimen; AML, acute myelogenous leukemia; ALL, acute lymphatic leukemia; CR1, first complete remission; CML, chronic myelogenous leukemia; CP, chronic phase; MDS, myelodysplastic syndrome; CY, cyclophosphamide; TBI, total body irradiation; BU, busulfan; HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease.
  †Patients who received single or multiple infusions of bulk donor buffy coat cells.
  ‡Patients who received escalating doses of donor buffy coat cells, based on the number of CD3+ cells. This group also comprised 6 patients receiving DLI prophylactically. §CR1 at time of HSCT; >CR1 at time of HSCT. ¶HLA-A, -B and -DR identical. §Nucleated cells × 10^9/kg recipient.

**Donor Leukocyte Infusions**

Donor cells were collected by leukapheresis on one or more occasions, depending on the cell yield. No donor was stimulated with growth factors before leukapheresis. BDR patients received cells fresh. For EDR patients, buffy coat
corresponding to $10^5$ to $10^6$ CD3$^+$ cells/kg recipient body weight constituted the initial cell dose. The remaining cells obtained from the leukapheresis were cryopreserved with autologous plasma and dimethyl sulfoxide in 1-log increments, with respect to the content of CD3$^+$ cells. Based on an estimated cell loss of 30% to 50% in the preservation procedure itself, the cell doses were doubled before freezing. A subsequent DLI dose was usually increased by 0.5 to 1 log.

Patients with CML in hematologic relapse were in some cases treated with hydroxyurea, but this drug was discontinued before DLI. Only occasional patients with acute leukemia were given pre-DLI chemotherapy. Different immunosuppressive and immunostimulatory regimens were used in conjunction with DLI, especially in the earlier years of the time studied. All patients had cyclosporin withdrawn when the relapse diagnosis was confirmed. Nine patients received GVHD prophylaxis with methotrexate (MTX) alone, 10 mg/m$^2$ intravenously, on days 1, 3, and 7 after DLI. Eight patients received MTX, as described above, in combination with various interleukin (IL)-2 regimens. In most cases, IL-2 was given in an initial infusion of 9 million units intravenously for 24 hours, followed by 2 million units subcutaneously/day for 4 weeks [24]. In a few cases, IL-2 was instead given in a dose of 6 million U/m$^2$ per day subcutaneously for 3 consecutive days [25]. Six patients were treated with IL-2 alone, whereas the remaining 21 patients received no immunomodulatory treatment in conjunction with DLI.

Patients were monitored with cytogenetic analyses on an individual basis after DLI, depending on the diagnosis. At each outpatient visit, full blood counts were taken to follow hematologic relapses. Patients with CML treated for molecular or cytogenetic relapse were checked with PCR for bcr/abl transcripts before each DLI and every 4 to 6 weeks after DLI.

**Diagnosis, Grading, and Treatment of GVHD**

Acute and chronic GVHD were diagnosed on the basis of clinical symptoms or verified by biopsies (skin, liver, gastrointestinal tract, or oral mucosa). Acute GVHD was graded on a scale from 0 to IV according to published criteria [26]. Grade 1 to II acute GVHD was treated with 2 mg/kg per day of prednisolone for 1 week, and the dose was then tapered [22,27]. In patients with progressive symptoms, prednisolone treatment was prolonged. For more severe cases, methylprednisolone (0.125 to 0.5 g/d), antithymocyte globulin, psoralen and ultraviolet A light (PUVA), or additional MTX was also given [27,28]. Chronic GVHD was graded as limited or extensive. The overall severity was defined as mild, moderate, or severe. Mild disease included sicca and minor symptoms affecting the skin and/or liver with a Karnofsky score of 90%. Moderate disease involved symptoms affecting 1 or several organs that could be controlled by immunosuppression but required prolonged or continuous therapy. The Karnofsky score in these patients ranged from 70% to 80%. Severe disease was defined as restricted functions, including such symptoms as malabsorption, sclerosis of the skin, severe bronchiolitis, etc., with Karnofsky scores below 70% [29,30]. Chronic GVHD was treated with cyclosporine and steroids. If a poor initial response was seen, some patients also received PUVA.

**Statistical Analysis**

Results were analyzed in April 2000, allowing for a median follow-up time of 38 months (range, 3-173 months). Time to relapse was analyzed from the time of DLI by the life-table method with the log-rank test (Mantel-Haenszel), taking censored data into account [31]. The definition of current leukemia-free survival (cLFS) implies living patients who are in remission following DLI treatment for a leukemic relapse. However, because the median time to a remission usually varies between 1 and 3 months [18] depending on the diagnosis, the patients in the cLFS analyses responding to DLI treatment had, to a varying degree, not yet re-entered remission during this initial time period. The patients receiving lymphocytes prophylactically (n = 6) were, by definition, not in relapse at the time of DLI and were therefore excluded from the survival analyses. For comparison of discrete data, the Fisher exact test was employed. Differences were considered significant when probability values were ≤ 0.05. Otherwise, they were considered nonsignificant (NS).

**RESULTS**

**Response to DLI and Duration of Remission**

Patients with CML had a cLFS of 46% at 3 years after DLI, compared with 13% at 18 months for patients with other diagnoses (P = .018) (Figure 1). However, as depicted in Figure 1, the maximum follow-up time for the latter patients was < 2 years. Of 22 treated CML patients, 15 (68%) re-entered CR after DLI. In this group, 4 of 5 patients treated by EDR responded (80%), compared with 11 of 17 patients (65%) treated by BDR (P = .54). At 3 years post-DLI, patients with cytogenetic (n = 10) or molecular (n = 3) relapse had a cLFS of 85%; patients with accelerated phase or hematologic relapse had a cLFS of 0% (P < .001) (Figure 2). Among 15 patients with CML initially responding to DLI, 4 patients subsequently relapsed within 2 years. A relapse occurred in 1 patient almost 9 years after DLI treatment. The median time from DLI to relapse of CML was 13 months (range, 1-104 months). Of 16 patients with acute leukemia, 4 (25%) responded and went into CR after DLI. Of these, 2 patients subsequently relapsed within 1 year after DLI. Patients with acute leukemia relapsing within 1 year of HSCT (n = 9) had 0% cLFS at 18 months, compared with 29% in patients with later relapses (P = .015) (Figure 3). No differences were seen between outcomes for patients with early (first CR) and later (beyond first remission) disease at HSCT. Furthermore, no significant differences in cLFS could be detected when comparing patients with different MTX/IL-2 regimens, but the individual groups were small. Among CML patients initially not responding to DLI, 4 of 5 patients with hematologic relapse and 0 of 2 patients with cytogenetic relapse had received MTX. Among CML patients subsequently relapsing after having achieved a remission (n = 5), 3 of 4 patients with an initial hematologic relapse had been given MTX after DLI, but not the 1 patient with cytogenetic relapse. Among the CML patients who responded and stayed in remission, 5 of 10 were given MTX after DLI.
GVHD, Thrombocytopenia/Neutropenia, and Causes of Death

Acute GVHD occurred in 12 of 43 evaluable patients (28%). Chronic GVHD occurred in 21 of 44 patients (48%). Table 2 shows the absolute incidences and the overall severity for acute and chronic GVHD for all patients and for patients treated by BDR or EDR. Although the incidence of GVHD grades II to IV was somewhat lower in the EDR group (8%) than in the BDR group (27%), this was not statistically significant (NS) \((P = .20)\). Patients who developed chronic GVHD after DLI showed a 3-year cLFS of 51% compared with 18% for patients without chronic GVHD \((P = .022)\) (Figure 4). Among the 15 patients who developed chronic GVHD, 10 patients had CML and 5 patients had non-CML disease. A separate analysis of patients with CML showed a 3-year cLFS of 69% in patients developing chronic GVHD \((n = 10)\) compared with 27% in patients without chronic GVHD \((n = 12)\) \((P = .058)\). Development of GVHD after the initial transplantation \((P = .18)\) and donor type (related or unrelated \([P = .59]\)) had no significant impact on the development of chronic GVHD after DLI. Furthermore, the development of acute

![Figure 1](image1.png)

**Figure 1.** Probability of current leukemia-free survival (cLFS) in chronic myelogenous leukemia (CML) patients compared with patients with other diagnoses (acute leukemia [AL] or myelodysplastic syndrome [MDS]). An event is either death or relapse. The initial drop in cLFS represents all patients not re-entering remission after donor lymphocyte infusion. The cLFS was measured from the time of donor lymphocyte infusion.

![Figure 2](image2.png)

**Figure 2.** Probability of current leukemia-free survival (cLFS) in patients with chronic myelogenous leukemia in cytogenetic or molecular relapse compared with patients with hematologic relapse. There were 10 patients in cytogenetic remission and 3 patients in molecular remission. The cLFS was measured from the time of donor lymphocyte infusion. An event is either death or a relapse. The initial drop in cLFS represents all patients not re-entering remission after donor lymphocyte infusion.
GVHD after DLI had no predictive value for the outcome. Patients with acute GVHD had a 3-year cLFS of 24% compared with 34% for patients without acute GVHD. Four of 17 patients receiving MTX after DLI developed acute GVHD grades II to IV, compared with 5 of 26 patients not given MTX (NS). The administration of IL-2 after DLI did not increase GVHD incidence compared with patients not receiving IL-2. None of the 6 patients receiving IL-2 treatment alone developed acute GVHD grades II to IV.

Thrombocytopenia, defined as platelet counts <30 $\times$ 10^9/L, occurred in 5 patients (11%); among those, 4 patients also developed neutropenia, with neutrophil counts <0.5 $\times$ 10^9/L. Of the 4 patients with neutropenia, 3 had acute leukemia and 1 had CML in accelerated phase. Among these, only 1 patient with acute leukemia achieved a lasting remission. Recurrent disease was the predominant cause of death (87%), followed by infection (9%) (Table 2). GVHD was a contributing cause of death in 6 patients (26%), comprising 4 patients with acute and 2 patients with chronic disease.

**DISCUSSION**

Recurrent disease remains one of the major causes of treatment failure after HSCT [32-34]. Regimens that have previously been used for the prevention and treatment of leukemic relapse include increased cytotoxic conditioning regimens [1,2], additional chemotherapy in combination with granulocyte colony-stimulating factor [35], and a second transplantation [3-6]. Unfortunately, results have been discouraging, with few long-term surviving patients. More recently, DLI has been shown to induce potent GVL effects and reinduce complete remissions. Initial response rates vary between 60% and 80% for patients with CML and between 10% and 20% for patients with acute leukemia [16,18-20].

Because treatment strategies and methods vary between centers and many of the previously published studies are based on data collected from a number of different centers, we evaluated the outcome after DLI therapy at our own institution. Because the response to DLI is clearly different in CML patients compared with other diagnoses, the results of the study may not be generalizable to all patients.

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**Table 2. Absolute Incidence of GVHD and Causes of Death After DLI**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>BDR†</th>
<th>EDR‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>31 (72)</td>
<td>20 (67)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Grade I</td>
<td>3 (7)</td>
<td>2 (7)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Grade II</td>
<td>5 (12)</td>
<td>5 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Grade III</td>
<td>3 (7)</td>
<td>2 (7)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Chronic GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>23 (52)</td>
<td>17 (57)</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Mild</td>
<td>10 (23)</td>
<td>5 (17)</td>
<td>5 (36)</td>
</tr>
<tr>
<td>Moderate</td>
<td>8 (18)</td>
<td>8 (27)</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (7)</td>
<td>0</td>
<td>3 (21)</td>
</tr>
<tr>
<td><strong>GVHD at death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>4 (17)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Chronic</td>
<td>2 (9)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cause of death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>2 (9)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Relapse</td>
<td>20 (87)</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>1 (4)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are n or n (%). GVHD indicates graft-versus-host disease; DLI, donor lymphocyte infusion; BDR, bulk dose regimen; EDR, escalating dose regimen.
†Patients receiving single or multiple infusions of bulk donor buffy coat cells.
‡Patients receiving escalating doses of donor buffy coat cells, based on the number of CD3+ cells. This group also comprised 6 patients receiving DLI prophylactically.
§Lost to follow-up.
are often stratified by diagnosis. Among our 22 patients with
CML, the initial response rate was 68%. However, during
the first 2 years, 4 patients relapsed, resulting in a 3-year
cLFS of 46%. One late relapse occurred almost 9 years after
DLI. Both the initial response rate and the proportion of
patients relapsing were somewhat higher than those
reported by Porter et al. [20] in a recent long-term follow-
up. There was a significant difference in cLFS between
CML patients in cytogenetic or molecular relapse and
patients with a hematologic relapse. In fact, none of
the patients with hematologic relapse achieved a durable remis-
sion (lasting more than a year) after receiving DLI. We
believe that the poor response rate in this group of patients
was not caused by unfavorable disease features, because only
2 patients were in accelerated-phase CML and the remain-
ning 7 patients were in chronic-phase CML.

One may speculate whether the various MTX regimens
used at our center have contributed to nonresponsiveness
after DLI, considering the absolute incidences of acute and
chronic GVHD were as low as 28% and 48%, respectively.
These rates of occurrence are lower than 41% [16] and 60%
[18] for acute and chronic GVHD, respectively, previously
reported in 2 large multicenter studies. Overall, we were not
able to detect a higher incidence of relapse among patients
receiving MTX compared with that of other patients. How-
ever, among CML patients with hematologic relapse, 4 of
5 patients not responding to DLI had received MTX after
DLI. Also, among CML patients with hematologic relapse—
initially re-entering CR but subsequently relapsing again—
3 of 4 patients had received MTX after DLI. However, the
various groups make it difficult to draw a firm conclusion
regarding the possible role of MTX in incidences of GVHD
and relapse. Our current belief is that immunosuppression
should be avoided at the time of DLI because the GVL
effect is most likely hampered by it.

For patients treated by EDR, 4 of 5 (80%) re-entered
remission after DLI, compared with 11 of 17 patients (65%) treated by BDR (NS). The group of patients treated by
EDR received a substantially lower total cell dose than that
received by patients treated by BDR (Table 1). On the other
hand, patients treated by EDR were all in cytogenetic or
molecular relapse, not hematologic relapse. It has been sug-
gested that patients with larger tumor cell burdens, as in the
case of a hematologic relapse, require larger DLI cell doses
than do patients in cytogenetic or molecular relapses
[15,17]. Our data, although not statistically significant, tend
to support this hypothesis. As expected, the incidence of acute GHVD grades II to IV tended to be lower (8%) in the
EDR group than in the BDR group (27%). This discrep-
ancy may be due to the lower number of cells given in the
EDR group, but as Dazzi et al. [17] recently showed, the
difference could also be due to the fact that cells given by
EDR are administered over a longer period. No difference
in the incidence of chronic GVHD could be seen between
the 2 dose regimens in our patients (57% and 43% in the
EDR and BDR groups, respectively [NS]).

When evaluating all 44 patients for cLFS, a significant
antileukemic effect was seen in patients with chronic GVHD,
compared with all other patients. The antileukemic effects
of chronic GVHD after HSCT are well known [10,34]. GVHD
secondary to DLI has also been shown to be closely associ-
ated with the response rate [16,18]. Our current study con-
firms this by showing a 3-year cLFS of 51% for patients with
chronic GVHD compared with 18% for all other patients
(P = .022). CML patients have been shown to be more prone
to chronic GVHD [36] and generally have a higher response
rate to DLI, which may contribute to the large discrepancy
seen here. On the other hand, a separate analysis of patients
with CML showed a 3-year cLFS of 69% in patients develop-
ing chronic GVHD compared with 27% in patients without
chronic GVHD. However, due to a low number of patients in
each group, this difference was of only borderline statistical
significance (P = .058). We saw no significant differences in
the outcomes for patients with or without acute GVHD.

Figure 4. Probability of current leukemia-free survival in patients developing chronic graft-versus-host disease (cGVHD) compared with all other patients (no cGVHD). DLI indicates donor lymphocyte infusion.
For patients with diseases other than CML, the outcome after DLI is less promising, with a DFS at 18 months of 13% in the current study. None of 9 patients diagnosed with a recurrent disease within 1 year after HSCT achieved a remission after DLI. For patients relapsing beyond 1 year after HSCT, the response rate was 29% at 18 months after DLI (P = .015).

These results clearly indicate the need for close monitoring, early diagnosis of recurrent disease, and aggressive treatment regimens for these patients. Innovative approaches that could limit the toxicity from DLI and potentially allow for a more intense cell therapy are needed. Augmenting the GVL effect by IL-2 administration has, in some cases, been successful [24,25,37]. Modification of donor T cells by suicide genes that can abrogate GVHD [38,39] and the selective depletion of CD8+ T cells from the donor product [40] are strategies currently being explored. The use of EDR will most likely be able to reduce the toxicity of DLI [17]. An alternative approach would be to expand and enrich cells with more direct antitumor effects. It has been shown that CML patients relapsing after HSCT have low numbers of NK cells compared with patients still in remission [41]. Because NK cells are also thought to be among the main effectors of the GVL effect [42], one may further explore the adoptive transfer of NK cells [43,44].

ACKNOWLEDGMENT

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