Effect of Low-Dose Interleukin-2 on Disease Relapse After T-Cell-Depleted Allogeneic Bone Marrow Transplantation

By Robert J. Soiffer, Christine Murray, René Gonin, and Jerome Ritz

T-cell depletion of donor bone marrow has been associated with an increased risk of disease relapse after allogeneic bone marrow transplantation (BMT). Recombinant interleukin-2 (IL-2), which is capable of increasing the antileukemic activity of peripheral blood lymphocytes obtained from patients who have undergone BMT, has been proposed as a potentially useful agent to reduce the risk of relapse post-BMT. We have previously shown that IL-2 administered to patients at very low doses after BMT is both clinically tolerable and immunologically active. We now report on the clinical outcome of 29 patients treated with low-dose IL-2 after CD6-depleted allogeneic BMT for hematologic malignancy. IL-2 was administered by continuous infusion for up to 3 months beginning at a median of 67 days post-BMT. Eligibility requirements for IL-2 therapy included demonstration of stable engraftment and absence of acute grade 2-4 graft-versus-host disease (GVHD). Low-dose IL-2 was well tolerated by the majority of patients, with only 4 of 29 subjects withdrawn early. Acute GVHD developed in only one individual. After 12 weeks of treatment, the mean number of circulating natural killer cells in patients increased 10-fold without any significant change in T-cell number. Of the 25 patients who received ≥1 month of IL-2, only 6 have relapsed. Relapse rate and disease-free survival (DFS) were determined in the 25 patients who completed at least 4 weeks of IL-2 treatment and compared with historical controls transplanted at our institution for the same conditions and treated with an identical ablative regimen and method of T-cell depletion. Only control patients who had survived disease free for 100 days post-BMT were included in this analysis. Cox's proportional hazards regression model suggested that, compared with control patients without a history of GVHD, patients treated with IL-2 had a lower risk of disease relapse (hazard ratio 0.34; range, 0.14 to 0.82) and superior DFS (hazard ratio 0.39; range, 0.18 to 0.87). A randomized controlled trial of IL-2 immunotherapy after T-cell-depleted BMT should now be undertaken.

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From the Divisions of Hematologic Malignancies and Biostatistics, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA.

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Address reprint requests to Robert J. Soiffer, MD, Dana-Farber Cancer Institute, 44 Binney St, Boston, MA 02115.

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with a history of relapsed acute leukemia, myelodysplastic syndrome (MDS), non-Hodgkin’s lymphoma (NHL), or accelerated phase chronic myelogenous leukemia (CML) were eligible for this study. After the relative safety of IL-2 infusion was established, inclusion criteria were broadened to include patients transplanted for acute leukemia in first remission and CML in stable phase. Pretreatment evaluation in all patients included a physical exam, complete blood count, serum chemistries, liver function tests, urinalysis, thyroid function tests, chest x ray, electrocardiogram, and pulmonary function tests. Eligibility criteria at the time of study entry included good performance status (ECOG 0-1) and near normal parameters of hepatic, liver, and pulmonary function. Absolute neutrophil count \(\geq 500 \times 10^6\) cells/\(\mu L\) with a platelet count \(\geq 40,000/\mu L\) independent of transfusion were required. All patients were required to be free of active infection at the time of protocol entry. All patients with evidence of active grades 2-4 GVHD were excluded from study, as were any patients receiving immune suppressive medications for GVHD or other indications. Written informed consent was obtained in all cases. The treatment protocol was approved by the Scientific Review and Human Subject’s Protection Committees at DFCI.

During the period between January 1990, when studies were begun, and February 1993, a total of 81 patients were transplanted for acute lymphoblastic leukemia (ALL) acute myeloid leukemia (AML), CML, MDS, or NHL at our institution. During this time, 29 patients were treated with IL-2. Of the 52 patients who did not receive IL-2 post-BMT, 14 were not eligible for treatment because they had grade 2-4 acute GVHD, 14 refused for logistical reasons, 8 were patients with early-stage acute leukemia or stable-phase CML who were transplanted when the treatment protocol was limited to patients with advanced disease, 6 had experienced early-disease relapse (before day +60), 6 had suffered toxic deaths (before day +60), 2 had poor performance status, and 2 had experienced graft failure.

**BMT protocol.** The transplant ablative regimen consisted of cyclophosphamide (60 mg/kg intravenous [IV]) on two consecutive days followed by 1,400 cGy total body irradiation delivered in seven equal 200 cGy fractions over 4 days. One patient who had received prior radiotherapy was instead treated with busulfan (16 mg/kg divided over 4 days) followed by cyclophosphamide (60 mg/kg IV \(\times 2\)). Twenty-eight patients who were treated with IL-2 had received bone marrow from an HLA-identical sibling donor. One patient received sibling marrow that was serologically mismatched at a single HLA locus. BM was collected by standard techniques. BM mononuclear cells were isolated and treated with anti-T12 monoclonal antibody (MoAb) (anti-CD6) and baby rabbit complement (Pel Freeze, Brown Deer, WI) as previously described. No patients received immunosuppressive therapy of any type for GVHD prophylaxis, including corticosteroids, methotrexate, or cyclosporine. After discharge from the hospital, patients routinely received multivitamin, folic acid supplementation, oral acyclovir for herpes simplex virus/varicella zoster virus (HSV/VZV) prophylaxis, and either oral trimethoprim-sulfamethoxazole or aerosolized pentamidine to prevent *Pneumocystis carinii pneumonia.*

**IL-2 therapy.** All patients received IL-2 by continuous intravenous infusion through an indwelling central catheter. Drug was delivered by a portable computerized ambulatory pump (Pharmacia/Detect Model 5100 HP; Pharmacia/Detect, St Paul, MN). The treatment was completely performed on an outpatient basis with one clinic visit each week. The supply of IL-2 was renewed every 7 days by the outpatient pharmacist. Recombinant IL-2 was provided initially by Hoffmann-LaRoche (Nutley, NJ; 24 patients) and, more recently by Amgen, Inc (Thousand Oaks, CA; 5 patients). Because some patients were treated as part of a phase 1 protocol, the starting dose varied from \(2 \times 10^4\) U/m²/d to \(6 \times 10^4\) U/m²/d. Planned duration of therapy was 3 months. Patients were not routinely treated with any prophylactic antipyretic or anti-inflammatory agents while on study. If patients had difficulty tolerating the initial dose level, therapy was temporarily interrupted and then resumed at a reduced dose level when symptoms abated. Doses were not escalated above the starting dose during the course of treatment.

**Immunophenotypic studies.** PBMC for immunologic studies were obtained weekly. Blood was collected in preservative-free heparin. PBMC were obtained after Ficoll-Hypaque (Pharmacia, Upssala, Sweden) density gradient sedimentation. PBMC were analyzed by direct immunofluorescence for reactivity with a series of MoAbs using standard techniques. Cells were analyzed for reactivity with a panel of MoAbs, including T3 (CD3), T4 (CD4), T8 (CD8), NKH1 (CD56), and Tac (CD25) (Coulter Immunology, Hialeah, FL). Immunofluorescence reactivity was determined by automated flow cytometry analyzing 10³ cells in each sample (ELITE, Coulter Electronics, Hialeah, FL).

**Statistical analysis.** The effects of IL-2 therapy upon risk of disease relapse and DFS post-BMT were evaluated in the 25 patients who completed at least 4 consecutive weeks of treatment. Comparison was made to historical controls transplanted at our institution for the same diseases and treated with a similar ablative regimen and method of T-cell depletion. Patients who died or relapsed \(\leq 100\) days post-BMT were not included in the control population because these patients would have been unlikely to have been eligible for IL-2 treatment. There were 92 patients who satisfied the above criteria. These 92 patients were then classified into two groups, depending on whether they did \((n = 23)\) or did not \((n = 69)\) have grade 2-4 GVHD post-BMT. Data were analyzed through September 1, 1993. Descriptive statistics are reported as proportions, medians, and means. Fisher’s exact test was used to compare proportions and the Kruskal-Wallis nonparametric analysis of variance test was used to compare the median follow-up time among the groups. Time to relapse (risk) and DFS curves for each subgroup were constructed by means of the Kaplan-Meier product limit method. The log-rank test was used to compare the various subgroups with respect to their time to relapse (risk) and DFS distributions in the univariate analyses. In a multivariable analysis, Cox’s proportional hazards regression model was used to determine possible predictors of relapse and DFS. The SAS procedure PHREG was used to compare proportions and the Kruskal-Wallis nonparametric analysis of variance test was used throughout. A test for proportional hazards using time-dependent covariates was conducted with respect to time to relapse (risk) and DFS. The proportional hazards assumption was not violated in both instances. The hazards ratios of each predictor (having adjusted for the effects of the other significant predictors) and 95% confidence intervals (CIs) for the hazards ratios were also calculated. All tests were two tailed.

**RESULTS**

**Patient characteristics.** There were 19 men and 10 women who received IL-2. Their median age was 41 years (range, 21 to 59 years). CML was the most common diagnosis for which patients underwent BMT \((n = 15)\), followed by AML \((n = 7)\), ALL \((n = 3)\), MDS \((n = 2)\), and NHL \((n = 2)\). Twelve patients were transplanted for either acute leukemia in first remission or CML in stable phase and were considered to have been transplanted at an “early” stage of their disease. The remaining 17 patients underwent marrow transplantation for more advanced disease. IL-2 was begun at a median of 67 days after marrow infusion (interquartile range, day +48 to day +104). The median white blood cell count at the initiation of IL-2 was \(4.2 \times 10^9/L\) and the median platelet count was \(121 \times 10^9/L\). Six patients began treatment...
with IL-2 at a dose of 2 × 10^5 U/m^2/d, 9 patients at 3 × 10^5 U/m^2/d, 11 patients at 4 × 10^5 U/m^2/d, and 3 patients at 6 × 10^5 U/m^2/d.

Toxicity of low-dose IL-2 after T-cell-depleted BMT.

The toxicities encountered during treatment with low-dose IL-2 after CD6-depleted allogeneic BMT are summarized in Table 1. The most common toxicities observed were fatigue, fever, nausea, and vomiting. Side effects were more frequently noted at the higher starting doses. Indeed, none of the 3 patients who were initially treated at 6 × 10^5 U/m^2/d were able to tolerate more than 2 weeks at this dose, largely because of constitutional and gastrointestinal symptoms. Overall, 25/29 patients were able to complete at least 4 weeks of therapy; 17/29 patients completed at least 8 weeks of treatment. Reasons for early discontinuation were catheter-related sepsis (3), bronchiolitis (2), gastrointestinal toxicity (2), disease relapse (2), pancytopenia (1), hypersensitivity (1), and acute GVHD (1). The source of IL-2 (Hoffmann-LaRoche, Amgen) did not appear to influence the frequency or severity of side effects. The single patient who developed acute GVHD had grade 3 disease, presenting with an erythematous rash and profuse watery diarrhea at 90 days post-BMT. The diagnosis was confirmed histologically with biopsies of the skin and sigmoid colon. GVHD developed 7 weeks after beginning IL-2 and persisted long after discontinuation. This patient later developed fatal Aspergillus pneumonia while receiving corticosteroids. Although several other patients did develop rashes while receiving IL-2, they were transient and usually resolved spontaneously. None of these patients had histologic evidence of GVHD when their skin was biopsied.

Immunologic effects. Immunophenotypic analysis of PBMC obtained from patients receiving IL-2 showed a selective increase in the number of circulating CD56⁺ NK cells without, in general, a change in CD3⁺ T-cell number (Fig 1). This contrasts sharply with the pattern of immunologic reconstitution observed in our non-IL-2-treated CD6-depleted allogeneic transplant recipients in whom no increase in circulating NK cells is observed beyond 6 weeks post-BMT. Dual-color immunofluorescence showed that the majority of NK cells noted in these patients coexpressed CD16 (FcγR, receptor) and lacked expression of CD3. Treatment with IL-2 did not induce expression of CD25, the low-affinity IL-2 receptor chain, on either NK cells or T cells. However, IL-2 therapy did increase the density of p75, the intermediate-affinity IL-2 receptor chain, on NK cells. Enhanced expression of the p75 IL-2 receptor chain was not induced on T lymphocytes at these dose levels of IL-2. Cytolytic activity against NK-sensitive and NK-resistant tumor targets was increased in all patients receiving IL-2. The timing of IL-2 initiation post-BMT appeared to influence the immunologic response. Figure 2 shows that patients in whom IL-2 was begun < 60 days post-BMT had more striking increase in both total lymphocytes (Fig 2A) and number of CD56⁺ NK cells (Fig 2B) than those in whom IL-2 was begun later. This phenomenon was independent of IL-2 dose and suggests that there may be a period after BMT during which NK cells are more susceptible to immunologic manipulation.

Patient outcome. Eighteen of the 25 patients who received ≥ 1 month of IL-2 therapy remain alive, free of disease at a median follow-up of 21 months post-BMT. Six patients have relapsed, 4 of whom received truncated courses of IL-2 because of side effects. The observed relapses occurred in 4 patients with AML transplanted in ≥ second complete remission, 1 patient with stable-phase CML, and 1 patient with MDS. Five of 14 patients (36%) who began IL-2 more than 2 months after BMT relapsed compared with only 1/11 (9%) patients in whom IL-2 was initiated within 2 months of BMT. None of the patients receiving low-dose IL-2 developed cytomegalovirus or any other viral infections after transplant.

Table 1. Toxicity of Low-Dose Recombinant IL-2 After T-Cell–Depleted BMT

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>N* (%)</th>
</tr>
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<tbody>
<tr>
<td>Fatigue</td>
<td>15 (52)</td>
</tr>
<tr>
<td>Fever (&gt;38°C)</td>
<td>14 (48)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>11 (38)</td>
</tr>
<tr>
<td>Myalgias</td>
<td>9 (31)</td>
</tr>
<tr>
<td>Rash</td>
<td>9 (31)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Edema/weight gain</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Catheter infection</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;20 × 10^9/L)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Neutropenia (&lt;0.5 × 10^9/L)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Azotemia (creatinine &gt;2.0 mg/dL)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Jaundice (bilirubin &gt;2.0 mg/dL)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypotension requiring pressors</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Includes all 29 patients treated with IL-2.
We compared the clinical outcome of patients receiving IL-2 with that of patients transplanted for the same malignancies at our institution since 1984. Control patients were treated with an identical method of donor-marrow T-cell depletion and ablative regimen. We separated controls into two groups of patients who either did or did not have evidence of grade 2-4 GVHD post-BMT, as the presence of GVHD would have precluded entry onto our IL-2 trial. We eliminated from the control groups all patients who either relapsed or died before day +100 post-BMT because these patients would have been unlikely to have been eligible for IL-2 treatment. Clinical variables were well balanced among IL-2–treated patients (group 1, n = 25) and control patients with (group 2, n = 23) or without (group 3, n = 69) grade 2-4 GVHD (Table 2). In particular, there were no significant differences among the groups with respect to patient age, diagnosis, or stage of disease at the time of BMT, although there was a predominance of males among patients who received IL-2. As expected, the median follow-up of control patients was longer than that of patients who received IL-2.

The probability of disease relapse for patients treated with IL-2 is displayed in Fig 3. Among patients without a history of GVHD, those who received IL-2 had a lower relapse rate than those who did not receive IL-2 (log-rank, \( P = .042 \)).

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The probability of disease relapse for patients treated with IL-2 is displayed in Fig 3. Among patients without a history of GVHD, those who received IL-2 had a lower relapse rate than those who did not receive IL-2 (log-rank, \( P = .042 \)).
In contrast, the presence of GVHD was not associated with patients undergoing allogeneic BMT, has been limited by a paucity of experimental evidence supports the proposition that T cells can mediate major histocompatibility complex (MHC)-restricted killing of tumor cells obtained from patients with early-stage disease. Allo-reactive T cells may exert their antileukemic activity directly against tumor targets or, indirectly, through the elaboration of secondary cytokines such as tumor necrosis factor, IL-1, or γ-interferon. The therapeutic application of donor T lymphocytes has been under recent investigation. There have been some preliminary reports indicating that infusion of T lymphocyte-rich buffy coat cells from HLA-identical allogeneic donors can induce hematologic and cytogenetic remissions in patients with CML who have relapsed post-transplant. However, buffy-coat infusion at the time of BMT, designed to induce GVL activity, has accomplished this goal remains unknown.

It is likely that the destruction of residual malignant cells post-BMT is mediated through several mechanisms, and some evidence suggests that, like T lymphocytes, NK cells may play an important role. In experimental models, NK cell number and activity have been found to correlate with resistance to metastatic spread of tumors. In humans, diminished NK cell function has been associated with cancer progression of both solid and hematologic malignancies. After allogeneic marrow transplantation, IL-2–activated NK cells can mediate major histocompatibility complex (MHC)-restricted killing of tumor cells obtained from patients before BMT. Therefore, it is possible that exploitation

### Table 3. Multivariate Analysis of Prognostic Factors: Risk of Relapse

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Estimated Coefficient</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2 + no IL-2 (group 1 vs. group 3)</td>
<td>-1.075</td>
<td>.016</td>
<td>0.34 (0.14-0.82)</td>
</tr>
<tr>
<td>GVHD + no GVHD (group 2 vs. group 3)</td>
<td>-1.006</td>
<td>.023</td>
<td>0.37 (0.15-0.87)</td>
</tr>
<tr>
<td>Advanced v early-stage disease</td>
<td>0.953</td>
<td>.001</td>
<td>2.59 (1.47-4.59)</td>
</tr>
<tr>
<td>Older v younger</td>
<td>0.581</td>
<td>.043</td>
<td>1.79 (1.02-3.14)</td>
</tr>
</tbody>
</table>

### Table 4. Multivariate Analysis of Prognostic Factors: DFS

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Estimated Coefficient</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2 + no IL-2 (group 1 vs. group 3)</td>
<td>-0.937</td>
<td>.021</td>
<td>0.39 (0.18-0.87)</td>
</tr>
<tr>
<td>Advanced v early-stage disease</td>
<td>0.783</td>
<td>.002</td>
<td>2.19 (1.32-3.63)</td>
</tr>
<tr>
<td>Older v younger</td>
<td>0.701</td>
<td>.007</td>
<td>2.01 (1.21-3.35)</td>
</tr>
</tbody>
</table>
of the cytotoxic activity of NK cells may be an effective way to approach the problem of preventing relapse posttransplant. In addition, because NK cells have been suggested to be important in the control of viral infection, their presence and activity may help to reduce some of the infectious complications typically observed after BMT.

The current study confirms that circulating NK cells can be safely expanded and activated in patients who have undergone T-cell-depleted allogeneic BMT. The absence of T-cell stimulation at these low doses probably accounts for the low incidence of GVHD observed during this trial. The contrasting response of T cells and NK cells to low-dose IL-2 derives from the distribution of IL-2 receptors on these cell types. The IL-2 receptor is comprised of several subunits with differing affinities for the cytokine. Resting T cells do not express the high-affinity heterodimeric receptor responsible for mediating the proliferative response to IL-2 whereas a fraction of resting NK cells have detectable high-affinity receptor on their surface. Moreover, the p75 chain of the IL-2 receptor, which binds IL-2 with intermediate affinity and may play a role in mediating cytolytic function, is expressed on virtually all resting NK cells, but not on resting T lymphocytes. Thus, by administering IL-2 in low doses rather than in the high doses characteristically used in immunotherapy trials for patients with metastatic renal cell carcinoma and melanoma, we can selectively manipulate NK cell number and function and avoid the induction of GVHD by activated T cells.

Multivariable analysis of our data indicates that, in patients without evidence of GVHD, treatment with IL-2 is associated with a reduction in the rate of disease relapse post-BMT. Because IL-2 has thus far not been administered in the context of a prospective randomized trial, the multivariate analyses in this study were necessarily performed on historical controls. These controls were comparable in terms of clinical characteristics and virtually identical in terms of clinical treatment. The exclusion of patients who had either relapsed or died within the first 100 days post-BMT eliminated from the control population patients who were unlikely to have been placed on IL-2 treatment. The reduction in the rate of disease relapse associated with IL-2 treatment was similar to that found in patients who developed GVHD after BMT at our institution. Notably, treatment with IL-2 was also associated with improved DFS compared with control patients who were free of GVHD. Despite the fact that control patients with GVHD relapsed less often than control patients without it, their overall DFS was not superior because of a higher incidence of fatal complications. Our data suggest that low-dose IL-2 therapy can provide a way to reduce the incidence of disease recurrence that is independent of GVHD and free of its toxic consequences. Moreover, our results provide further evidence in support of an important role for NK cells in the GVL process.

Despite these encouraging results, it still remains unclear exactly how to maximize the immunologic effects of low-dose IL-2 therapy. We have observed that dose escalation may be difficult because of the development of intolerable side effects. As doses of IL-2 are increased, the selective stimulatory effect on NK cells will ultimately be lost because of saturation of intermediate-affinity receptors on other cell types. Efforts should be directed at discovering ways to further activate the NK cell compartment already expanded by low-dose IL-2, perhaps by exposure to other immunomodulatory agents such as IL-12, IL-6, or ionomide. The appropriate duration of treatment with IL-2 is also uncertain.

Previous trials of IL-2 post-BMT have involved high doses of therapy for relatively short intervals. In contrast, low-dose IL-2, because it is well tolerated, can be continued for an extended period. Prolonged immune stimulation may be important to the GVL phenomenon as witnessed by the strong association between de novo chronic GVHD and freedom from posttransplant disease relapse. However, the inconvenience of maintaining central venous catheters and their susceptibility to infection may make prolonged treatment problematic. Alternative routes of IL-2 administration (ie, subcutaneous) need to be examined to determine if they can produce equivalent degrees of selective NK cell expansion and activation post-BMT.

The appropriate timing of IL-2 initiation post-BMT also must be ascertained. Animal studies have suggested that the beneficial effect of IL-2 may be lost if it is not administered close to the time of marrow infusion. Our preliminary findings suggest a more robust NK cell response with earlier initiation of treatment. There may be a window of opportunity in which IL-2 therapy is immunologically and clinically most effective. However, it is not clear that patients can tolerate IL-2 in the very early posttransplant period. A recent report on the administration of IL-2 to patients with ALL after autologous BMT showed that early treatment produced considerable toxicity.

Like recipients of T-cell-depleted allogeneic marrow, patients undergoing autologous BMT are at higher risk of relapse than those undergoing unpurged allogeneic BMT. Because the pace and character of lymphoid reconstitution differ between recipients of autologous and T-cell-depleted allogeneic marrow, it is not certain that the immunologic responses to IL-2 will be identical. Nevertheless, our previous studies have shown that the NK cell response to low-dose IL-2 is similar in these two groups. Although no conclusions have been drawn regarding the efficacy of IL-2 in the autologous BMT setting, one group has suggested that it lowers the relapse rate of patients undergoing auto-BMT for AML. IL-2 administration might also be useful after unpurged allogeneic BMT for patients with advanced malignancies at high risk of relapse. However, it has not as yet been extensively studied, partially because it is feared that IL-2 would induce severe GVHD. Because low-dose IL-2 appears to selectively activate NK cells, and not T lymphocytes, this approach would be worth investigating in this setting. However, it is possible that allo-reactive T cells, present after unpurged allo-BMT, but generally absent after T-cell-depleted BMT, would be stimulated at lower doses of IL-2 because of the presence of high-affinity IL-2 receptors on their surface. Any clinical trials with IL-2 after unpurged allo-BMT must be undertaken with caution.

It is hoped that the restoration of GVL activity after T-cell-depleted allogeneic marrow transplantation will lead to an improvement in long-term DFS for patients with hematopoietic malignancies.
logic malignancies. Our results suggest that low-dose IL-2 administration for a prolonged period post-BMT may help to accomplish this goal.

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