Phase II Study of Autologous Transplantation with Interleukin-2–Incubated Peripheral Blood Stem Cells and Posttransplantation Interleukin-2 in Relapsed or Refractory Non-Hodgkin Lymphoma

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ABSTRACT

Previous work suggested that interleukin (IL)-2 can be used for eradicating residual disease in autologous grafts and for preventing recurrence. We report a phase II study of autologous peripheral blood stem cell transplantation with in vitro IL-2 incubation of peripheral blood stem cells and posttransplantation IL-2 in patients with recurrent or refractory non-Hodgkin lymphoma. Salvage chemotherapy consisted of ifosfamide and etoposide. Responding patients underwent autologous peripheral blood stem cell transplantation. IL-2–incubated stem cells were infused on day 0. IL-2 1 mIU/m2 was given from day 1 until day 28. Four monthly maintenance cycles of IL-2 4 mIU/m2 subcutaneously twice daily days 1 to 5 and days 8 to 11 were administered thereafter. Eighty-four evaluable patients were enrolled, and 60 proceeded to transplantation, of which 56 received IL-2–incubated stem cells. The average received dose of posttransplantation IL-2 was 30% to 50% of planned. Only 42 patients received maintenance IL-2. The average received maintenance dose of IL-2 was also approximately 30% of planned. Most dose reductions were due to toxicity or patient refusal. Three-year survival and progression-free survival for all registered patients were 43% (95% confidence interval [CI], 33%-53%) and 31% (95% CI, 21%-41%), respectively. For the 60 patients undergoing transplantation, they were 59% (95% CI, 46%-72%) and 44% (95% CI, 31%-57%), respectively. There was no relation between the dose of IL-2 received and outcome. Survival and disease-free survival of the study group were similar to those of a previous study cohort that received unmanipulated stem cells and no systemic IL-2. Administration of IL-2–incubated peripheral blood stem cells and intensive posttransplantation IL-2 was associated with considerable but rapidly reversible toxicity. No effect on long-term outcome was observed.

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KEY WORDS

Peripheral blood stem cells • Interleukin-2 • Non-Hodgkin lymphoma • Survival

INTRODUCTION

High-dose chemotherapy with autologous transplantation is the treatment of choice for patients with recurrent lymphoma, but it is effective in only a minority of patients because of a high incidence of disease recurrence [1-3]. Lymphomas are also sensitive to immunotherapy, as indicated by their responses to interferon [4-6] and in particular to interleukin (IL)-2 [7,8]. Although IL-2 has activity as a single agent, it does not induce durable responses when used in patients with established disease, and it has long been thought that the optimal use for it might be in the setting of minimal residual disease, as is commonly achieved after high-dose chemotherapy [9].

We have studied in vitro incubation of stem cells with IL-2 followed by immediate posttransplantation administration of systemic IL-2. A potential advantage of this approach is that the in vitro incubation with IL-2 might have a “purging” effect; ie, it might lead to
the eradication of occult lymphoma cells contained in the stem cell graft that otherwise might contribute to disease recurrence. Indeed, murine experiments indicate that the administration of IL-2–incubated stem cells, followed by posttransplantation IL-2, resulted in a powerful antileukemic effect [9,10]. We initially demonstrated the feasibility of this approach in patients with leukemia and lymphoma [11]. Here we present the results of a phase II study in patients with recurrent lymphoma.

**PATIENTS AND METHODS**

**Eligibility Criteria**

Patients between the ages of 15 and 65 years with relapsed or refractory intermediate-grade, low-grade, or immunoblastic lymphoma were eligible. Those with mantle-cell lymphoma and transformed lymphoma were also eligible. Documentation of histology at the time of relapse by biopsy or fine-needle aspiration cytology was recommended but not required. The laboratory requirements were as follows: absolute granulocyte count >1.5 × 10^9/L, platelet count >100 × 10^9/L, bilirubin <1.2 mg/dL, serum creatinine <2.0 mg/dL (unless due to disease), human immunodeficiency virus antibody negative, and no evidence of active hepatitis or cirrhosis.

The organ function requirements were as follows: performance status of ≤2, no symptomatic heart disease, diffusion capacity of the lung for carbon monoxide ≥50% of predicted, forced expiratory volume in 1 second ≥50% of predicted, no active connective tissue disorder, no history of seizures, and no pleural effusion, pericardial effusion, or ascites, unless caused by lymphoma. Patients were excluded if they had evidence of central nervous system involvement at relapse.

The protocol was approved by the institutional review boards at the M.D. Anderson Cancer Center and at the University of Illinois at Chicago, and voluntary written, informed consent was obtained from each patient before beginning the protocol treatment.

**Treatment**

Salvage chemotherapy consisted of 1 to 3 cycles of ifosfamide and etoposide [2] (Table 1). Upon recovery from the first or second treatment cycle, stem cell apheresis was performed. Patients underwent frequent re-staging between cycles, and when a maximal response (complete response [CR], stable partial response [PR], and in some cases a minor response) was achieved, they proceeded to transplantation. Ifosfamide/etoposide consisted of the following: before chemotherapy patients received mesna 2 g/m^2 intravenously (IV) over 2 hours. This was followed by ifosfamide 3.3 g/m^2/d mixed with mesna 2.66 g/m^2/d in continuous infusion for 3 consecutive days (total dose of ifosfamide 10 g/m^2). After the ifosfamide was completed, patients continued to receive mesna 2 g/m^2 by continuous infusion for 12 hours. Patients also received etoposide 150 mg/m^2 IV over 2 hours every 12 hours for 3 consecutive days (the total dose of etoposide was 900 mg/m^2).

After every course of chemotherapy, patients received subcutaneous granulocyte colony-stimulating factor 5 μg/kg daily. This dose was doubled to 5 μg/kg twice daily after the course of ifosfamide/etoposide that was used for stem cell mobilization. After treatment with ifosfamide/etoposide, patients received oral quinolones, fluconazole, and acyclovir until recovery of neutrophil counts. Packed red blood cells were administered for hemoglobin <8 g/dL, and platelets were administered for a platelet count <20 × 10^9/L. All blood products were filtered and irradiated. The target cell dose for stem cell mobilization was 8 × 10^6 CD34+ cells per kilogram. At least 3 × 10^6 CD34+ cells per kilogram were to be kept as a backup, and the rest were to be used for in vitro incubation.

**Conditioning Regimens**

The conditioning regimen for patients with intermediate-grade, transformed, or immunoblastic lymphoma was BEAM chemotherapy. BEAM consisted of carmustine 300 mg/m^2 IV over 1 hour on day −6; etoposide 200 mg/m^2 IV over 6 hours every 12 hours on days −5, −4, −3, and −2 (total of 8 doses); cytarabine 200 mg/m^2 IV over 30 minutes every 12 hours on days −5, −4, −3, and −2 (total of 8 doses); and melphalan 140 mg/m^2 IV on day −1. Patients received an infusion of peripheral blood stem cells on day 0.
Patients with low-grade lymphoma were preferably given a total body irradiation (TBI)—containing regimen consisting of etoposide 1500 mg/m² IV on day –8, cyclophosphamide 60 mg/kg IV over 2 hours on days –7 and –6, and TBI. TBI 12 Gy was administered in 4 daily fractions of 3 Gy on days –4, –3, –2, and –1 with lung shielding.

**Thawing and Activation of Peripheral Blood Progenitor Cells on Day –1**

Each bag of cryopreserved peripheral blood progenitor cells (PBPC) was thawed rapidly in a 40°C water bath. Cell count, viability, Gram stain, culture, and assays for colony-forming units were performed on a small aliquot of the thawed product. The culture bags for incubation of PBPC with IL-2 were prepared by adding each 50-mL aliquot of PBPC from the thawed cryopreservation bags to a 1-L incubation bag containing RPMI 1640 medium with the following additives: 1-glutamine 2 mmol/L, β-mercaptopetothanol 5 × 10⁻⁵ mol/L, gentamicin 0.05 mg/mL, deoxyribo-nuclease 0.2 mg/mL, heparin 50 U/mL, IL-2 6000 IU/mL, and 10% autologous plasma that had been collected and frozen at the time of stem cell harvest. The cell concentration in this incubation mixture was 3 × 10⁶/mL.

After 18 to 24 hours of incubation in a 5% CO₂ incubator, the contents of each bag were harvested and washed in the cell separator with the RPMI 1640 medium containing 5% autologous plasma.

**Peripheral Blood Stem Cell Infusion**

The product was reuspended in approximately 250 mL of autologous plasma and infused over approximately 1 hour while vital signs were closely monitored. Patients were premedicated with diphenhydrane 25 mL IV, meperidine 50 mg IV, and acetaminophen 650 to 1000 mg by mouth. Corticosteroids were avoided. A small portion of the cell suspension was used for the Gram stain and endotoxin assay to be performed immediately before reinfusion.

**Granulocyte-Macrophage Colony-Stimulating Factor**

Granulocyte-macrophage colony-stimulating factor 250 µg/m² (subcutaneously or IV daily) was started on day 1 after transplantation and was continued until the absolute neutrophil count reached 1 × 10⁹/L for 3 consecutive days.

**IL-2 Therapy**

**Posttransplantation IL-2.** IL-2 was started 24 hours after the infusion of autologous activated stem cells to allow for the potential toxicities of the infusion to resolve. The initial IL-2 dose was 1 mIU/m²/d by continuous IV infusion, and this infusion was to be continued for 21 days. Patients discharged before day 21 could be switched to an equivalent subcutaneous dose.

**Maintenance IL-2.** A 1-week rest period was provided after completion of the initial low-dose IL-2 infusion. Thereafter, the IL-2 dose was escalated to 4 mIU/m² subcutaneously twice daily for 5 days followed by a 48-hour rest interval and another 5-day treatment. This 12-day treatment cycle was repeated approximately every month for a total of 4 cycles.

**IL-2 Toxicities and Dose Adjustment.** Strict guidelines for the management of IL-2 toxicities and dose adjustments during the postinfusion (hematologic reconstitution) period could not be provided, because many of the clinical and laboratory complications during this time were similar to the toxicities of IL-2 in the nontransplant setting. A general guideline for the withholding of therapy and potential resumption at dose decrements of 50% was based on the judgment of the treating physician and of the principal investigator as to the contribution of IL-2 to serious toxicities.

The National Cancer Institute common toxicity criteria were used for the assessment of IL-2 toxicities, as defined previously. IL-2 was to be withheld for any serious organ toxicity that was not easily managed with standard supportive care such as antiemetics, antipyretics, and IV fluids or for any medical complication of the transplantation to which IL-2 was judged to be contributing. If such toxicity resolved within 72 hours and was not considered life-threatening or attributable to IL-2, then IL-2 could be resumed at 50% of the original dose. Recurrence of similar toxicities was an indication for discontinuation of IL-2.

**Posttransplantation Evaluation and Response Criteria**

Response to therapy was evaluated after every treatment course; approximately 3 months, 6 months, and 1 year after transplantation; and annually thereafter. Evaluation consisted of physical examination; blood counts; chest radiograph; computed tomography of the chest, abdomen, and pelvis; and marrow aspirate and biopsy for those with a history of bone marrow involvement. Gallium scanning, although routinely used, was not considered in the formal assessment of response. Additional tests—such as immunophenotyping of the blood and bone marrow, lymph node aspiration, or biopsy—were performed when clinically indicated. CR was defined as the disappearance of all clinical and radiologic evidence of active tumor. PR was defined as a ≥50% decrease in the sum of the products of all measured lesions. Stable disease was defined as no change in the size of the measurable lesions or a response that was less than a partial remission and no progression for a minimum of 8 weeks. There could be no appearance of new lesions for this category.
Statistical Design and Analysis

This was a single-arm phase II study. Sample size was calculated with the method of Dixon and Simon [12]. We estimated that an accrual of approximately 72 patients would provide sufficient power to reject the null hypothesis of 30% long-term disease-free survival observed in a historical cohort. Primary outcomes analyzed were progression-free and overall survival. Probabilities of primary outcomes were calculated with the Kaplan-Meier product-limit estimate [13] and expressed as probabilities with a 95% confidence interval (CI).

Because our main interest was in identifying the role of IL-2 incubation and posttransplantation IL-2 on the outcome of transplantation, the analysis was restricted to the subset of patients who, after a response to salvage therapy, underwent transplantation. In this cohort, we evaluated the importance of the following covariates: disease histology, disease response (CR versus PR versus minimal response), number of prior treatments, dose of IL-2 received after transplantation, and percentage of planned IL-2 received during maintenance therapy. Because of the limited patient number, no multivariate analysis was attempted. Univariate comparisons used the log-rank test [14]. To evaluate the effect of IL-2 incubation on outcome, the data were combined with those from a previous study with similar eligibility criteria, salvage therapy, and conditioning regimen. In this historical control group, patients did not receive posttransplantation IL-2 or IL-2–incubated stem cells [2].

RESULTS

Patient Characteristics

Ninety-five patients were enrolled between April 1997 and July 2000. Eighty were enrolled at the M.D. Anderson Cancer Center and 15 at the University of Illinois at Chicago. Two patients were ineligible because of erroneous diagnosis (1 Hodgkin disease and 1 Burkitt lymphoma), 1 because of a history of chronic myelogenous leukemia, and 2 because of thrombocytopenia before enrollment. Six were not evaluable because they received nonprotocol treatment. Among the 84 evaluable patients, there were 44 men and 40 women, with a median age of 47 years (range, 18-65 years). Fifty-seven patients had diffuse large B-cell lymphoma, 9 had primary mediastinal B-cell lymphoma, and 8 had follicular lymphomas. Four patients had mantle-cell lymphoma. Four patients had anaplastic large-cell lymphoma, and 3 had other types of peripheral T-cell lymphoma. All patients had either recurrent or refractory disease. Ninety-four percent had a good performance status, but one third had increased serum lactate dehydrogenase. Twenty percent had primary refractory disease, and the rest had either first or second recurrence. Forty-three percent of the patients were enrolled at the time of documentation of recurrence, and the ifosfamide/etoposide regimen was used as the salvage regimen. They were therefore “untested” recurrences. The remainder of the patients were enrolled after receiving some other form of chemotherapy to which they were sensitive (44%) or refractory (12%). As a result, 11% of the patients were already in complete remission at enrollment.

Ifosfamide/Etoposide

As previously reported, the ifosfamide/etoposide regimen is a highly myelosuppressive, but effective, regimen, and only 18 (22%) of the 84 patients did not respond [2]. Six patients with responsive disease did not proceed to transplantation, in four cases because of prolonged myelosuppression and a resulting inability to collect stem cells. One patient had severe cardiac complications that precluded transplantation, and 1 patient refused to proceed with transplantation.

Autologous Transplantation and Posttransplantation IL-2

Sixty patients proceeded to transplantation. Fifty-seven received conditioning with BEAM, and 3 received conditioning with cyclophosphamide/etoposide TBI (Table 2). Stem cells incubated with IL-2 were infused on day 0 in 56 patients. Four patients received nonincubated stem cells because the collected stem cell dose was insufficient. As previously
reported [11] and as summarized in Table 3, fever and chills were frequently associated with the infusion of these stem cells. Mild, reversible hypotension also occurred in 17% of patients. Reversible hypoxia occurred in 10%. Arrhythmias occurred in 3 patients, and temporary transfer to the intensive care unit was necessary in 2. The cells had been washed to remove IL-2 and dimethyl sulfoxide before reinfusion. The toxicities are therefore attributable to direct effects of the incubated cells. All toxicities were mild: no grade 3 toxicities occurred.

Posttransplantation IL-2 was started in all patients, but the dose often had to be reduced because of subjective intolerance and fever.Received doses are summarized in Table 4. Only a third of the patients received the full planned dose of IL-2, and most received between 30% and 50% of the planned dose. By comparison, the average received dose in our phase I study was 74%. Hypotension, chest pain, and renal failure occurred in 1 patient each. There were no treatment-related deaths in the first month after transplantation.

Maintenance IL-2

Forty-two patients started the first cycle of maintenance IL-2. Twenty-eight patients received all 4 planned cycles, 5 received 3 cycles, 4 received 2 cycles, and 5 received only 1 cycle. Dose reductions were also common, and only 4 patients received all of the planned maintenance treatment. The median received dose was approximately 30% of planned, consistent with observations in the phase I study. Reasons for dose reduction or discontinuation were progressive disease in 3 patients, sepsis in 1 patient, toxicity in 35 patients, and refusal in 11 patients.

A total of 140 cycles of maintenance IL-2 were administered, but toxicity information was available for only 121 of these cycles and is summarized in Table 5. Fever was extremely common. Mild GI toxicity (nausea, diarrhea, and vomiting) was common, as were headaches and lethargy. Usually such toxicities were rapidly reversible with dose reduction or discontinuation. There was 1 documented seizure, 1 case of pulmonary emboli, and 1 case of severe liver and severe gastrointestinal toxicity. One case of cryofibrinogenemia and skin necrosis has been separately reported [15]. Gram-negative sepsis occurred during 5% of the maintenance courses and was fatal in 1 case.

Survival and Disease-Free Survival: Effect of IL-2 Treatment and IL-2 Incubation

With a median follow-up of 40 months (range, 13-55 months), the estimated 3-year survival and progression-free survival are 43% (95% CI, 33%-53%) and 31% (95% CI, 21%-41%), respectively, for the entire study population (ie, all 84 eligible patients). This is similar to what we observed in previous studies [2,16].

In the subgroup of 60 patients who proceeded to transplantation, there was only 1 treatment-related death, which was due to sepsis after a course of maintenance IL-2. Estimated survival and disease-free survival in patients undergoing transplantation were 59% (95% CI, 46%-72%) and 44% (95% CI, 31%-57%), respectively. We could not detect a correlation between days of posttransplantation IL-2, cumulative dose of posttransplantation IL-2, or the cumulative percentage of maintenance IL-2 and progression-free survival (Figures 1 and 2).

In an additional analysis, we attempted to assess the effect of IL-2 incubation of stem cells on long-term outcome. For that purpose, we combined the data on our study patients with those of a previous study of an ifosfamide/etoposide regimen followed by autologous stem cell transplantation with unmanipu-

| Table 3. Grade I and II Toxicities Related to Infusion of IL-2–Incubated Stem Cells |
|-----------------|---|
| Toxicity         | %  |
| Fever            | 18% |
| Chills           | 27% |
| Hypotension      | 17% |
| Arrhythmia       | 6%  |
| Hypoxia          | 10% |
| Transfer to intensive care unit | 4% |

| Table 4. Cumulative Dose of IL-2 Received in the First 21 Days (as a Percentage of the Planned Dose) |
|-----------------|---|
| Planned Dose %  | % Received |
| 10%-30%         | 5%          |
| 30%-50%         | 55%         |
| 50%-90%         | 20%         |
| 100%            | 30%         |

| Table 5. Toxicities and Infections Occurring during Administration of Maintenance IL-2 (121 Episodes) |
|-----------------|-----------------|-----------------|
| Variable        | NCI Toxicity Grade |
|                 | 1               | 2               | 3               | 4               |
| Nausea/vomiting | 35 (29%)        | 4 (3%)          | 0               |
| GI              | 17 (14%)        | 2 (2%)          | 1 (1%)          |
| Liver           | 1 (1%)          | 0               | 1 (1%)          |
| Pulmonary       | 6 (5%)          | 2 (2%)          | 1 (1%)          |
| Renal           | 2 (2%)          | 6 (5%)          |                 |
| CNS             | 22 (19%)        | 12 (10%)        | 1 (1%)          |
| Skin            | 9 (7%)          | 6 (5%)          |                 |
| Infections      |                 |                 |                 |
| Gram-negative sepsis | 6 (5%)    |                 |                 |
| Gram-positive sepsis | 2 (2%)    |                 |                 |

NCI indicates National Cancer Institute; CNS, central nervous system.
lated stem cells [2]. Forty-five patients participated in that study, of whom 35 proceeded to transplantation. Combining the 2 groups resulted in a study cohort of 95 patients undergoing transplantation. Ninety-one of these received BEAM conditioning, and 56 received IL-2–incubated stem cells. The characteristics of both study groups were similar, as summarized in Table 2. There were no significant differences in progression-free survival between those receiving IL-2–incubated stem cells and those receiving unmanipulated stem cells (Figure 3).

**DISCUSSION**

Dose intensification with hematopoietic stem cell rescue after conventional salvage therapy is the standard of care for patients with recurrent lymphoma and is particularly effective in patients whose lymphoma has responded to salvage chemotherapy [1,17]. Recurrences after autologous transplantation account for a large proportion of the treatment failures and may be explained by 2 mechanisms: (1) failure of the high-dose conditioning regimen to eradicate the underlying disease and (2) recurrence derived from occult lymphoma cells contained in the stem cell graft. The strategy pursued in our trial was meant to address these 2 issues simultaneously. IL-2 is a potent stimulator and survival factor for T cells and natural killer (NK) cells and probably derives its antitumorefficacy from its immunostimulatory effects [7,8,18-20]. It may have its major effect in situations of minimal residual disease achieved after high-dose chemotherapy. Furthermore, the immunologic reconstitution after autologous or allogeneic stem cell transplantation is characterized by an early recovery of NK cells followed by somewhat delayed T-cell recovery, with a preponderance of cytotoxic T cells [21-24]. This early posttransplantation environment may be particularly suitable for the effects of IL-2 [25]. However, IL-2 has considerable systemic and potential hematopoietic toxicity [26], which may be exacerbated in the weeks after high-dose chemotherapy [27]; therefore, in many trials, its administration has been delayed until after hematopoietic recovery. Studies of posttransplantation IL-2 have been conducted in both the allogeneic and autologous transplant settings. Varying doses and schedules have been evaluated [9,27-37]. Biological activity is well documented, but the only group to report a substantial benefit from posttransplantation IL-2 was the Hadassah group. They administered high doses of IL-2 in combination with interferon starting 2 to 10 months after transplantation for aggressive lymphoma and Hodgkin disease, and they reported excellent tolerance and a survival benefit when compared with historical controls [38]. The treatment was delayed for up to 10 months after transplantation in this study and therefore was almost certainly limited to a rather favorable-risk group of pa-

![Figure 1](image1.png)  
**Figure 1.** Progression-free survival after transplantation for patients who received IL-2–incubated peripheral blood stem cells. The effect of cumulative doses of posttransplantation IL-2 received is shown.

![Figure 2](image2.png)  
**Figure 2.** Progression-free survival after transplantation for patients who received IL-2–incubated peripheral blood stem cells. The effect of maintenance doses of IL-2 is shown.

![Figure 3](image3.png)  
**Figure 3.** Progression-free survival after transplantation. The effect of incubation of peripheral blood stem cells (PBSC) with IL-2 and administration of posttransplantation IL-2 is shown.
tients. In addition, IL-2 was combined with interferon, and it is conceivable that most of the activity resulted from the interferon, which previously has been shown to improve survival in lymphoma [5,39]. The use of posttransplantation IL-2 was also evaluated in 2 randomized studies. The Southwest Oncology Group is conducting a randomized study of posttransplantation IL-2 in lymphoma that is nearing completion. A French cooperative group study of posttransplantation IL-2 in acute lymphatic leukemia in first remission showed no benefit [40].

A slightly different approach consists of stimulating NK cell precursors in bone marrow or stem cells in vitro with IL-2 in an attempt to increase antitumor activity and to purge the graft of contaminating cells [41-43]. In vitro stimulated lymphokine-activated killer cells lack hematopoietic toxicity but seem to be able to selectively deplete malignant cells [44-49]. The feasibility and in vitro efficacy of this technology were validated by several groups [48,50-55]. We tested this in our initial phase I study of 32 patients with hematologic malignancies, and we found reasonable tolerance and rapid hematopoietic reconstitution after transplantation [11]. We were able to administer an average of 70% of a planned dose of 1 × 10^6 IU/m^2/d of IL-2 in the first 21 days after transplantation, as well as 30% of a planned maintenance dose of 6 × 10^6 IU/m^2/d for 10 days every month for 4 months. The initial results in lymphoma patients were particularly encouraging, with 9 of 19 patients with advanced refractory disease surviving disease free [56].

The patient selection criteria, chemotherapy induction, and transplant conditioning regimen of the subsequent phase II study were modeled after a prior study of salvage chemotherapy at M.D. Anderson [2]. An identical ifosfamide-based induction was used, as was a consolidation with BEAM chemotherapy. It was therefore anticipated that patients participating in the prior study would serve as historical controls. Response rates to salvage chemotherapy and tolerance to posttransplantation IL-2 were similar to what we had previously observed, although the ability to administer the posttransplantation IL-2 was slightly reduced, perhaps because of the higher median age of patients in the phase II study. Considerable symptomatology was attributed to IL-2 and consisted mainly of fever, general malaise, and skin rashes. Severe side effects also occasionally occurred after infusion of the IL-2–incubated stem cells, similar to what others have observed [37]. Life-threatening side effects related to cell infusion or IL-2 were rare. The IL-2–related symptoms led, however, to frequent dose reductions or even patient refusal to continue the treatment.

Disappointingly, the long-term outcome of our patients was not different from that observed in previous studies, and we failed to detect an effect of the dose of IL-2 received during maintenance treatment or immediately after transplantation on the outcome of the transplantation. We attempted to analyze the effect of the complete treatment strategy (ie, the sequence of stem cell incubation with IL-2 followed by in vivo IL-2) by pooling the data with outcome data from our historical controls and also failed to detect an effect on relapse rates. Our results are reminiscent of the report by Burns et al. [37], who used lymphocytes that were obtained by apheresis, incubated in vitro with IL-2, and then reinfused to autologous transplant patients with either metastatic breast carcinoma or lymphoma. In a second cohort of patients, they infused bolus doses of IL-2 as an alternative to cell therapy. Despite marked biologic effects, they did not observe any clinical benefit from either of these approaches.

The failure of immunotherapy with IL-2 to affect recurrence rates in these studies, despite biological activity, may be explained in a number of ways. It could be due to an inappropriate dose or schedule of administration of posttransplantation IL-2. One article suggests that both low and high doses of IL-2 are associated with a lack of activation [25]. Weisdorf et al. [27] used a similar dose of IL-2 after transplantation and found serum levels of 5 to 20 U/mL, which was sufficient only to stimulate the very-high-affinity receptors [57]. The planned regimen of IL-2 used in our trial was, however, more intense than in most other trials and turned out not to be practical in many patients; dose reductions were often required, and unless novel methods are identified to reduce the toxicity of IL-2, it is unlikely that further dose escalation will be possible. In this regard, the recent description of a selective inhibitor of IL-2 toxicity is of particular interest [58,59]. It is also possible that we failed to detect a true effect (type II error), a risk that is somewhat increased by the use of a historical control group, which may have failed to take into account an unrecognized imbalance in prognostic features. Still, if this were the case, any true effect of our intervention on recurrence rates is likely to have been small.

The failure of our trial underscores the need for innovative approaches to improve outcome after autologous transplantation. IL-2, because of its biologic effects, continues to have considerable interest and has, for example, been combined with rituximab to increase antibody-dependent cellular cytotoxicity [60]. A combination of IL-2, rituximab, and granulocyte-macrophage colony-stimulating factor given as posttransplantation therapy is currently being tested at our institution.

In summary, this is, to our knowledge, the largest prospective phase II trial of posttransplantation IL-2 and IL-2–incubated stem cells for patients with recurrent lymphoma. Toxicity was considerable but usually rapidly reversible. No effect of this strategy on long-
term outcome was observed. We conclude that stem cell transplantation with IL-2–incubated peripheral blood stem cells and posttransplantation IL-2 given in this fashion is unlikely to result in major benefits for patients with recurrent lymphoma.

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