



Transplantation of IL-2-mobilized autologous peripheral blood progenitor cells for adults with acute myelogenous leukemia in first remission

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In order to improve leukemia-free survival we evaluated the feasibility and efficacy of autologous transplantation of interleukin-2 (IL-2)-mobilized peripheral blood progenitor cells for adult patients with acute myelogenous leukemia in first remission. Forty-nine consecutive patients (median age 49, range 21–70) with acute myelogenous leukemia in first remission were enrolled on a study of high-dose cytarabine/mitoxantrone consolidation chemotherapy with post-recovery IL-2 used as a method of *in vivo* purging for the purpose of autologous peripheral blood progenitor cell transplantation. A median of 2.08×10^6 CD34⁺ peripheral blood progenitor cells/kg were infused 1 day after preparative conditioning with 11.25 Gy total body irradiation and cyclophosphamide (120 mg/kg). Forty-one patients received myeloablative chemoradiotherapy followed by the infusion of IL-2-mobilized autologous peripheral blood progenitor cells. The median times to both neutrophil and platelet recovery were 16 days (range, 2–43) and 23 days (8–318+ days), respectively. Twenty-seven patients remain alive with 24 in continued first complete remission. Median remission duration for all eligible patients is 8 months, and actuarial leukemia-free survival is $49 \pm 15\%$. The actuarial risk of relapse is $43 \pm 16\%$. Toxicity of autologous peripheral blood progenitor cell transplant included treatment-related death in three patients and serious organ toxicity in 12. Advanced age was a negative prognostic factor for leukemia-free survival. Results were compared to an age-matched historical control treated with autologous transplantation of chemotherapy-mobilized progenitor cells; no significant difference in favor of IL-2 mobilization could be demonstrated. Our results demonstrate that autologous transplantation of IL-2-mobilized peripheral blood progenitor cells is feasible in an unselected population of adult patients with acute myelogenous leukemia in first remission with minimal toxicity but no clear evidence of benefit in leukemia-free survival. *Leukemia* (2001) 15, 757–763.

Keywords: acute; myelogenous; leukemia; interleukin; transplantation; autologous

Introduction

In order to prolong leukemia-free survival, a variety of post-remission treatment strategies such as myelosuppressive maintenance therapy, multiple and prolonged cycles of consolidation chemotherapy, autologous and allogeneic bone marrow transplantation have been evaluated for patients with acute myelogenous leukemia in first complete remission.^{1–3} Although potentially most effective in reducing the risk of relapse, allogeneic bone marrow transplantation from an histocompatible sibling donor is associated with a high risk of treatment-related mortality and is available only to a limited population of younger patients with generally favorable disease characteristics.⁴ Autologous bone marrow transplantation allows for the use of dose-intensive preparative conditioning without the high risk of treatment-related complications or the immunologic risks associated with allogeneic transplantation

and is available to a larger, unselected population of patients. When evaluated prospectively, autologous bone marrow transplantation for adult patients with acute myelogenous leukemia in first complete remission has produced leukemia-free survival in the range of 30 to 50%; treatment-related mortality is generally in the range of 10 to 20%.^{5–7} In a previous study of high-dose cytarabine-based consolidation chemotherapy followed by autologous transplantation of chemotherapy-mobilized peripheral blood progenitor cells, we demonstrated the feasibility of this post-remission treatment approach in an heterogeneous population of adult leukemia patients not restricted on the basis of younger age, the availability of an histocompatible donor, or other favorable prognostic features. Toxicity was limited to myelosuppression with very low treatment-related mortality and actuarial leukemia-free survival of $42 \pm 14\%$. This represents a significant improvement when compared to results we achieved with consolidation chemotherapy alone. The major limitation of autotransplantation in our study was leukemia relapse, most likely due to proliferation of chemotherapy-resistant leukemia cells that survived induction and consolidation chemotherapy as well as myeloablative preparative conditioning.⁸

In order to prolong leukemia-free survival we sought to build on the favorable results of post-remission autologous transplantation by incorporating interleukin-2 (IL-2), a novel immunostimulatory drug with single-agent activity in acute leukemia. IL-2 is a growth factor for T lymphocytes and natural killer (NK) cells which acts in part to control neoplastic populations of cells.^{9,10} Laboratory investigations have supported the hypothesis that IL-2 can stimulate cytotoxic effector cells capable of eradicating residual leukemia.¹¹ IL-2 has been used therapeutically to induce regression in certain malignant tumors and is already well established in the treatment of renal cell carcinoma and malignant melanoma.¹² In acute leukemia, IL-2 has been given as a single agent for relapsed disease, and has been used to incubate autologous progenitor cells *in vitro* for the purpose of transplantation. In the present study, we examined the feasibility of administering IL-2 *in vivo* after both consolidation chemotherapy and transplantation. We used IL-2 as a mobilizing agent for peripheral blood progenitor cell procurement and analyzed the effect of transplantation of these IL-2-mobilized progenitor cells followed by post-transplant IL-2 maintenance on leukemia-free and overall survival. We specifically sought to examine the clinical efficacy of this unique form of autologous transplantation in an heterogeneous population of adult leukemia patients not restricted on the basis of young age or other favorable disease features. We also analyzed the effect of major pretreatment characteristics including age, gender, history of pre-leukemia, abnormal cytogenetics and IL-2 treatment on therapy-related complications as well as leukemia-free survival, comparing our results to an historical group of patients undergoing autologous transplantation without IL-2 immunomodulation.⁸

Patients and methods

Fifty-six adult patients with newly diagnosed acute myelogenous leukemia in first complete remission were enrolled on the ALP (Acute Leukemia Protocol) 6 Study conducted by the UCLA School of Medicine from 3 February 1997 to 7 February 2000. Data were analyzed as of 15 May 2000. Median follow-up from the time of bone marrow remission for surviving patients eligible for consolidation and transplantation is 23 months (range, 4–39 months). This study design was approved by the UCLA Human Subject Protection Committee and all patients provided written informed consent to participate.

The diagnosis of acute myelogenous leukemia was made according to French–American–British (FAB) criteria.¹³ *De novo* acute myelogenous leukemia was defined if no documented hematologic abnormality was identified more than 2 months before diagnosis.¹⁴ Pre-leukemia was defined as ineffective hematopoiesis documented more than 2 months before the diagnosis of acute myelogenous leukemia by either an abnormal bone marrow evaluation or an otherwise unexplained peripheral blood cytopenia.^{2,14} Patients with leukemia secondary to treatment for another malignancy were not eligible to participate in this study. Karotype was classified as follows: (1) normal, ie diploid; (2) abnormal but favorable, ie t(8;21), or abnormalities of 16q; (3) abnormal and unfavorable, ie trisomy 8, abnormalities of chromosomes 5 and/or 7, any abnormality of chromosome 11, multiple (>3 abnormalities) or complex translocation; and (4) abnormal all others or not done. Patients with acute promyelocytic leukemia, with or without t(15;17), were not eligible for this study.

Fifty-six patients had received induction chemotherapy consisting of cytarabine, 100 to 200 mg/m²/day by continuous infusion for 5 to 7 days and idarubicin, 10 to 13 mg/m²/day by i.v. bolus for 3 days (49 patients), daunorubicin, 45 to 60 mg/m²/day by i.v. bolus for 3 days (six patients), or doxorubicin, 45 mg/m²/day i.v. for 3 days (one patient). Nine patients received a second course of induction chemotherapy on or after day 21 if residual acute leukemia was found in blood or bone marrow. Complete hematological remission was defined as previously.⁸

Consolidation chemotherapy consisted of cytarabine, 2 g/m² administered as 2-h i.v. infusion every 12 h for 4 days and mitoxantrone, 10 mg/m² by i.v. bolus daily for 3 days. Recombinant human G-CSF was administered at 5 µg/kg subcutaneously or i.v. over 30 min beginning 1 day following completion of consolidation and continued until the completion of stem cell leukapheresis. Recombinant human IL-2 therapy (Chiron Corporation, Emeryville, CA, USA), 3 million units/m² subcutaneously twice daily for 10 days, was begun on the first day of hematopoietic recovery (defined as absolute neutrophil count ≥ 1000 mm⁻³) both after consolidation chemotherapy and again after autologous transplantation. Of the 56 patients entered at first complete remission, 49 were eligible for consolidation chemotherapy and autologous peripheral blood progenitor cell transplant on basis of age ≤ 70 and no organ dysfunction. Results of these 49 patients form the group under analysis and are included in analysis of remission duration, disease-free survival and survival on the basis of intention-to-treat. Forty-one eligible patients completed autologous stem cell transplant of IL-2-mobilized peripheral blood progenitor cells after preparative conditioning with 11.25 Gy total body irradiation given in five fractions over 2.5 days and cyclophosphamide 60 mg/kg/day by i.v. infusion over 1 h daily for 2 days. Patients received mesna, 60 mg/kg/day by continuous i.v. infusion at the start of cyclo-

phosphamide and continued for 24 h after the last dose. After hematologic recovery from transplantation, maintenance IL-2 was initiated at the same dose and schedule as after consolidation. Toxicity was scored according to standard criteria.

Progenitor cell collection and processing

Progenitor cell apheresis was begun after an absolute neutrophil count of >1500 mm⁻³ was achieved during the recovery phase from consolidation therapy. Continuous-flow leukapheresis was performed daily on weekdays with a Cobe Spectra (Cobe, Lakewood, CO, USA) until a total nucleated cell count of $\geq 5 \times 10^8$ /kg and/or CD34 cell count $\geq 1 \times 10^6$ /kg was obtained. Total blood volume processed per run was 10 l at a flow rate of 50–70 ml/min. Platelet and erythrocyte fractions were re-infused continuously. The final apheresis product was centrifuged at 400 g, reconstituted to a concentration of 10^8 cells/mm³, and cooled to 4°C. Cytogenetics were analyzed on an aliquot of the leukapheresis collection in patients undergoing progenitor cell procurement by taking 0.01–0.03 ml of the stem cell suspension sample and placing it directly into flasks containing 10 ml RPMI 1640 culture medium supplemented with 1 ml cell growth factor.⁸ After remaining in culture for 24–48 h, two drops of ethidium bromide (0.01 mg/ml) were added to each flask for 30 min. One drop of colcemid (10 µg/cm³) (Life Technologies, Grand Island, NY, USA) was added for an additional hour. Cells were then swollen in a hypertonic solution of 0.4% potassium chloride for 15 min and fixed in Carnoy's fixative. After subsequent centrifugation and washing of cells with fresh fixative the cell suspension was applied to slides, banded with trypsin, and then stained with Giemsa in order to perform a metaphase analysis. The remainder of the stem cell collection was cryopreserved daily in 10% dimethylsulfoxide by control-rate freezing and stored in the gas phase of liquid nitrogen. Cell counts were performed using a Coulter counter (Coulter Electronics, Hialeah, FL, USA). A target mononuclear cell dose of 5×10^8 /kg and/or CD34 cell count $\geq 1 \times 10^6$ /kg was used as an endpoint for collection. Samples were analyzed on a FACScan flow cytometer (Becton Dickinson, San Jose, CA, USA) and CD34-positive cells were defined with histogram analysis using the whole live-cell population. No back-up bone marrow was collected.

Results on the basis of intention-to-treat from the time of complete remission were compared to an age-matched control group assigned to receive high-dose cytarabine consolidation and autologous transplantation of unmanipulated, chemotherapy-mobilized autologous peripheral blood progenitor cells without immunotherapy in a study conducted from 1992 to 1996.⁸

Supportive care

Supportive care for granulocytopenic patients consisted of reverse isolation in single rooms and treatment with oral non-absorbable antibiotics including nystatin and either norfloxacin or ciprofloxacin. Febrile granulocytopenia patients received imipenem or cefoperazone/sulbactam, or other broad-spectrum antibacterial antibiotics. Patients with documented or suspected fungal infections were treated with empiric amphotericin B or fluconazole. Random or single-donor platelet transfusions were administered to maintain a

platelet count $\geq 10 \times 10^9/l$. Erythrocytes were transfused to maintain a hematocrit $\geq 27\%$.

Statistical analysis

The date of diagnosis of AML and the date of remission were defined by the diagnostic bone marrow studies. Patients were analyzed for overall survival as well as leukemia-free survival (LFS) from the time of remission by the product-limit method of Kaplan and Meier.¹⁵ Univariate comparisons of patients undergoing induction and consolidation chemotherapy were performed using the chi-square test and the Wilcoxon rank-sum test.¹⁶ Summary estimates included survival fractions \pm two times the standard error for 95% confidence intervals for median survival times.^{15,16} Survival curves were compared using the log-rank test. Prognostic factors for survival and leukemia-free survival (LFS) were evaluated using the Cox regression analysis. Analysis was performed using the SAS statistical package.¹⁶ *P* values were two-sided throughout.

Results

Forty-nine patients age ≤ 70 were eligible for autologous transplant following consolidation chemotherapy with high-dose cytarabine, recombinant human granulocyte colony-stimulating factor (rHuG-CSF) and, upon recovery, recombinant human IL-2 (rHuIL-2) given for the purpose of *in vivo* purging and procuring of IL-2-mobilized autologous progenitor cells. The median duration of follow-up for surviving patients from the time of complete remission is 19 months (range, 4–38 months). Patient characteristics are described in Table 1. Toxicity of consolidation chemotherapy included serious neurotoxicity due to high-dose cytarabine in one patient and treatment-related death in three patients due to infection (one patient) and multiorgan system failure (two patients), respect-

Table 1 Patient characteristics

	No.
No. of patients	49
Sex (M/F)	21/28
Age (median, range)	49 (21–70)
Median WBC $\times 10^9/l$ at diagnosis (range)	12 (1–232)
Chromosome abnormality (Yes/No/Other)	23/20/6
History of preleukemia (Yes/No/Other)	17/30/2
Original diagnosis	
Undifferentiated	10
Myelogenous	5
Promyelocytic	2
Myelomonocytic	23
Monocytic	1
Erythroleukemia	1
Unknown	2
Other	5
No. of patients (years) (age)	
≤ 45	20
46–60	13
> 60	16
Karyotype favorability	
Normal	21
favorable	6
unfavorable	12
All others	10

Sex had one missing observation, and WBC had four.

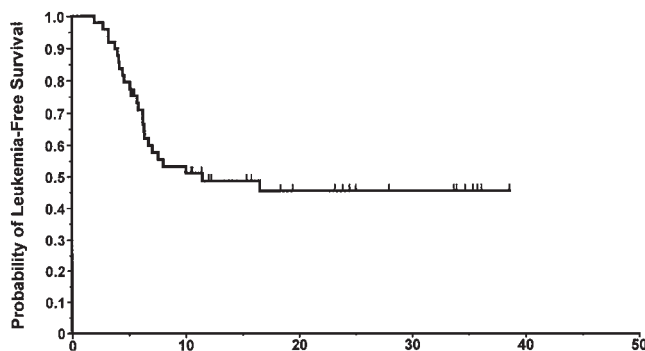


Figure 1 Leukemia-free survival in 49 patients assigned to undergo autologous transplantation of IL-2 mobilized progenitor cells.

ively. Of 49 eligible patients, five did not undergo autologous peripheral blood progenitor cell collection due to physician/patient preference (two patients), treatment-related morbidity and mortality (two patients) and early relapse (one patient). Another three patients underwent progenitor cell collection but did not undergo transplantation due to patient preference, early death, and inadequate cell collection (one each). A median of four collections (range, 1–14) were required to procure a median of 8.56×10^8 total mononuclear cells/kg (range, 2.15 – $22.54 \times 10^8/kg$). A median of 2.08×10^6 CD34-positive progenitor cells/kg (range, 1.02 – $31.27 \times 10^6/kg$) were infused after a preparative regimen of total body irradiation and high-dose cyclophosphamide. The median number of doses of IL-2 given after both consolidation chemotherapy and autologous transplantation was 20. IL-2-related toxicity included flu-like symptoms in most patients with frequent nausea and vomiting. Serious organ dysfunction attributable to IL-2 consisted of cardiac and pulmonary problems occurring in three patients and one patient, respectively. After transplantation, the median times to neutrophil $> 500 \text{ mm}^{-3}$ and untransfused platelet $> 20000 \text{ mm}^{-3}$ were 16 days (range, 12–43) and 23 days (range, 8–318+), respectively. Complications related to transplantation included serious organ toxicity in 12 patients with treatment-related mortality in three patients due to pneumonia (two patients), colitis and multi-organ system failure (one patient). Twenty-seven of the 49 patients (55%) remain alive with 25 in continued first remission from 4 to 38 months. Median remission duration at the time of analysis is 8 months (range, 2–38 months), and actuarial leukemia-free survival is $49 \pm 15\%$ (Figure 1). Median survival from remission is 10 months (range, 2–38 months) and actuarial survival from remission is $56 \pm 15\%$ (Figure 2). Nineteen

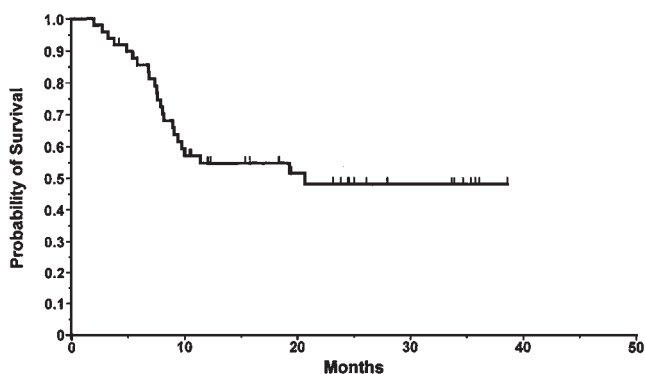


Figure 2 Overall survival in 49 patients assigned to undergo autologous transplantation of IL-2-mobilized progenitor cells.

(39%) have relapsed with an actuarial risk of relapse of 43 ± 16% (median time to relapse 8 months). Patients received further intensive chemotherapy and two achieved a second remission. Four patients underwent allogeneic bone marrow transplant and there are no long-term survivors with median survival from second transplant 54 days. Median survival after relapse was 2 months (range, 1–22 months). Of the 41 patients who actually underwent autologous transplantation of IL-2-mobilized progenitor cells, median disease-free and overall survival are 10 and 11 months, respectively. Actuarial disease-free survival from remission for the transplant patients is 56 ± 16%.

Advanced age was an adverse predictive factor for leukemia-free survival ($P = 0.0137$) (Table 2). The median leukemia-free survival for all 29 patients over age 45 (22 of whom underwent transplant) vs 20 patients age ≤45 years (all of whom underwent transplant) was 7 months and 15 months, respectively. The actuarial leukemia-free survival 1 year from complete remission for all eligible patients over the age of 45 is 36 ± 20% as opposed to 65 ± 21% for patients ≤45 years of age. The log-rank test of the two age groups resulted in a P value of 0.0607 for disease-free survival. Ten of 16 eligible patients over age 60 underwent transplant; the actuarial disease-free survival for this group was considerably lower, 36 ± 26%.

When adjusting for age, pre-leukemia history was also pre-

dictive ($P = 0.03$) for disease-free survival. Adjusting for age, a history of preleukemia was not significant in multivariate analysis. Pretreatment characteristics such as gender, original diagnosis, and pretreatment leukocyte count also did not achieve statistical significance in multivariate analysis after adjusting for age. Note, however, that results regarding the analysis of karyotype favorability were inconclusive. No patient with a favorable cytogenetic abnormality sustained a relapse. In a multi-variate analysis of leukemia-free survival, other pre-treatment characteristics did not achieve statistical significance (Table 2).

Abnormal cytogenetics were identified in 10 leukapheresis collections, but all 41 patients underwent autologous transplantation. Normal cytogenetics were identified in 18 patients and the remaining samples were either not obtained (five patients) or did not grow (eight patients). Abnormal cytogenetics in the leukapheresis collections did not confer an increased risk of relapse.

Results for the 49 patients on the present study were compared to an age-matched historical control group (ALP 5) with similar pretreatment characteristics assigned to receive high-dose cytarabine-based consolidation chemotherapy followed by chemotherapy-mobilized autologous peripheral blood progenitor cell transplantation (Table 3). Only preleukemia history was found to be significantly different for the two groups. Comparing survival of the two groups and adjusting for age,

Table 2 Univariate analysis for disease-free survival

Variables	No. of subjects	No. of events	Median survival	Risk ratio	95% CI	DF	P value
Total	49	24	11.466	—	—		
Age (continuous)	49	24	—	1.040	1.007, 1.073	1	0.0137
Age							
≤45	20	7	—	0.357	0.137, 0.933	2	0.0930
(46–60)	13	6	11.466	0.615	0.226, 1.676		
>60	16	11	7.064	—	—		
Sex							
Male	21	9	—	—	—	1	0.5503
Female	28	15	7.589	1.286	0.562, 2.940		
Chromosome abnormality							
No	20	10	10.021	1.346	0.294, 6.165	2	0.9212
Yes	23	12	11.466	1.351	0.301, 6.069		
Other	6	2	—	—	—		
Preleukemia history							
No	30	13	—	—	—	1	0.0073
Yes	17	11	5.848	2.933	1.291, 6.667		
Original diagnosis							
Undifferentiated	10	6	13.273	0.238	0.066, 867	7	0.0001
Myelogenous	5	3	6.538	0.310	0.068, 1.408		
Promyelocytic	2	1	—	0.344	0.038, 3.125		
Myelomonocytic	23	6	—	0.130	0.036, 0.471		
Monocytic	1	1	5.749	1.156	0.124, 10.8		
Erythroleukemia	1	1	3.220	7.808	0.615, 99.179		
Unknown	2	2	5.026	1.442	0.252, 8.239		
Other	5	4	4.041	—	—		
WBC	45	21	—	1.004	0.996, 1.013	1	0.2864
Karyotype favorability							
Normal	21	10	—	2.810	0.615, 12.830	3	0.1243
Favorable/Not done/Unknown	11	2	—	—	—		
Unfavorable	12	9	6.357	5.247	1.131, 24.346		
All others	5	3	12.057	3.730	0.623, 22.353		

Table 3 Comparison of patient characteristics

Variables	Historical	Treatment	P value
Median age	56	49	0.1835
Age			0.5870
≤45	19	20	
(46–60)	14	13	
>60	24	16	
Sex			0.5240
Male	29	21	
Female	28	28	
Chromosomal abnormality			0.2650
Normal	21	21	
Favorable	2	6	
Unfavorable	20	12	
All others	14	10	
History of preleukemia			0.0120
Yes	21	17	
No	23	30	
Other	13	2	
Original diagnosis			0.2670
Undifferentiated	14	10	
Myelogenous	16	5	
Promyelocytic	1	2	
Myelomonocytic	16	23	
Monocytic	3	1	
Erythroleukemia	1	1	
Unknown	1	2	
Other	5	5	
Median WBC at diagnosis	18	12	0.7163

there were no significant differences in leukemia-free and overall survival that could be identified on the basis of differences in the post-remission treatments.

Discussion

The optimal post-remission therapy to prevent or to delay leukemia relapse still remains uncertain. One to several courses of intensive high-dose cytarabine-based consolidation chemotherapy remains the least toxic regimen against which other dose-intensive strategies are compared.^{1,17,18} Older patients and patients with leukemia arising out of myelodysplasia are felt not to benefit from any one specific post-remission strategy on the basis of a high likelihood of recurrence.^{2,19,20} Unfortunately, allogeneic transplantation has not been clearly demonstrated to offer a significant improvement in survival even for those with adverse pre-treatment characteristics.^{4,21,22} Autologous transplantation of previously collected cryopreserved bone marrow or peripheral blood progenitor cells allows for the administration of myeloablative conditioning equivalent to allogeneic transplantation but to a heterogeneous population of patients with acute myelogenous leukemia in first remission. In randomized trials this treatment has been limited in part by poor compliance.^{5–7,23} We have previously shown that a preparative regimen consisting of total body irradiation and high-dose cyclophosphamide was well-tolerated regardless of patient age and can produce a high likelihood of leukemia-free survival even in a population of patients with unfavorable prognostic features. Neutrophil and platelet recovery were rapid, and after a median follow up of 27 months, the actuarial leukemia-free and overall survival were 42% and

54%, respectively. The results of this study demonstrate that autologous transplantation of chemotherapy-mobilized peripheral blood progenitor cells is feasible in an unselected population, producing a high likelihood of leukemia-free survival with minimal toxicity.⁸

The major cause of post-remission treatment failure is relapse, most likely due to proliferation of leukemia cells that survive induction, consolidation and preparative conditioning. Allogeneic transplantation may decrease the risk of relapse through a mechanism of adoptive immunotherapy.²⁴ IL-2 has been identified as a possible immune therapy providing for just such an immune effect without the need for an allogeneic graft.^{11,20,25} Foa *et al*²⁶ reviewed the pre-clinical trials which gave experimental support for using IL-2 to treat acute leukemia. These studies demonstrated that IL-2 may eradicate murine leukemias,^{27,28} that leukemia cells may be lysed or their growth may be inhibited by IL-2-activated effector cells,^{29,30} and that IL-2 only rarely induces growth of acute leukemia cells.³¹ Clinical trials have also shown some anti-leukemia activity for IL-2 in patients with advanced AML.³² Some reports demonstrate that patients with residual leukemia blasts after conventional therapy could be induced into remission with IL-2 treatment.³³ These encouraging results in patients with more advanced AML led to the studies of IL-2 in maintaining remission at a stage of residual disease. Although a small study of nine patients with AML treated after achieving first complete remission failed to show benefit, IL-2 was started at variable time intervals making results difficult to interpret.³⁴ Several phase I studies have analyzed the effect of IL-2 following autologous bone marrow transplant in an effort to reproduce the favorable features of adoptive immunotherapy associated with allogeneic transplantation. The results demonstrate that IL-2 may be capable of inducing a high number of effector cells against autologous leukemia cells.^{26,35,36}

The objective of the present analysis was to build on previous autologous transplantation experience by incorporating IL-2. We also studied the effect of IL-2 on the delivery of chemotherapy and growth factor-induced mobilization of peripheral blood stem cells. We assessed the rate of engraftment after reinfusion of these IL-2-mobilized cells in patients, many with unfavorable pre-treatment characteristics representative of the general population of patients with acute myelogenous leukemia, undergoing myeloablative conditioning. Forty-one of 49 eligible patients actually underwent the autologous transplantation procedure using chemotherapy/G-CSF and IL-2-mobilized peripheral blood progenitor cells after a preparative regimen of total body irradiation and high-dose cyclophosphamide. Maintenance IL-2 was initiated after hematologic recovery at the same dose and schedule as had been given after consolidation.

The treatment was well tolerated. The duration of transplant-induced neutropenia and thrombocytopenia was acceptable and transplant-related morbidity and mortality were comparable when compared to previous autologous transplant experience.^{5–7,37} Interleukin2-related toxicities consisted of flu-like symptoms, fever, nausea, vomiting, diarrhea, fatigue, confusion, dizziness, rash, chest pains, irregular heart beat, altered pulmonary function, altered renal function, and altered liver function. After a median follow-up from remission of 15 months, actuarial leukemia-free survival is 60 ± 15%. Median survival from remission is also 15 months and actuarial survival from remission at 1 year is 56 ± 15%. The addition of IL-2, however, did not eliminate the influence of adverse pretreatment characteristics on leukemia-free survival. Age and cytogenetics were significant prognostic factors sug-

gesting that despite good tolerance to treatment, high-dose chemo-radiotherapy and autologous transplantation of IL-2-mobilized progenitor cells could not overcome the effect of disease biology.

Results on the basis of intention-to-treat were compared to an age-matched historical control group with similar pre-treatment characteristics assigned to receive high-dose cytarabine-based consolidation chemotherapy followed by chemotherapy-mobilized autologous peripheral blood progenitor cell transplantation without any immunomodulation.⁸ No significant difference could be demonstrated suggesting that despite its potential effect on minimal residual diseases, this study was unable to demonstrate a favorable impact of post-remission IL-2 on progression-free survival.

Despite the hazards of interpreting results from any individual non-randomized phase II study, several investigators using a variety of doses and schedules of IL-2 have come to similar conclusions. In a study of 50 patients with acute lymphoblastic leukemia in first complete remission treated with autologous transplantation, Blaise *et al*³⁸ administered high-dose recombinant IL-2 at different dose levels over five cycles. A high degree of immune stimulation, as documented by natural killer and T cell proliferation, was demonstrated. The 3-year leukemia-free survival was 41%, which did not represent an improvement when compared to results achieved for patients receiving autologous transplantation without immunotherapy. In acute lymphoblastic leukemia, IL-2 has been given after autologous bone marrow transplants for patients in second or subsequent remission and has not been shown to delay or prevent relapse.³⁹ Finally, in a pilot trial of IL-2-treated autologous bone marrow transplantation followed by maintenance IL-2, long-term leukemia-free survival was achieved in only two of 12 patients with acute lymphoblastic leukemia and three of nine patients with acute myelogenous leukemia.⁴⁰

Immunotherapy, if active, should be most effective in the elimination of minimal residual disease after autologous bone marrow transplantation. This approach is under investigation and is the subject of randomized trials. Unfortunately, no single dose or delivery system has been demonstrated to be most effective in improving survival or in altering surrogate biologic endpoints such as the elaboration of cytotoxic T lymphocytes. No satisfactory endpoints have currently been demonstrated that would allow the determination of a dose-response relationship. The absence of a favorable clinical response in any one study does not imply that in a sufficiently powered, phase III randomized trial a benefit may not be achieved for one or more of these treatment regimens.

Incorporating new agents that are designed to eliminate subclinical disease holds promise in improving progression-free survival for acute myelogenous leukemia in first remission. A pharmacologic approach to effect this anti-leukemia activity remains an important component of clinical investigation.

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