



Interleukin-2 after autologous stem cell transplantation for hematologic malignancy: a phase I/II study

N Robinson, MC Benyunes, JA Thompson, A York, S Petersdorf, O Press, C Lindgren, T Chauncey, CD Buckner, WI Bensinger, FR Appelbaum and A Fefer

Division of Medical Oncology, Department of Medicine, University of Washington, the Fred Hutchinson Cancer Research Center and the Veterans Affairs Medical Center, Seattle, WA, USA

Summary:

The success of autologous stem cell transplantation (ASCT) for hematologic malignancy is limited largely by a high relapse rate. It is postulated that IL-2 administered after ASCT may eliminate minimal residual disease and thereby reduce relapses. A phase I/II study was performed to identify a regimen of IL-2 (Chiron) that could be given early after ASCT in phase III trials. In the phase I study, beginning a median of 46 days after ASCT for hematologic malignancy, cohorts of three to four patients received escalating doses of 'induction' IL-2 of 9, 10, or 12×10^6 IU/m²/day for 4 or 5 days by continuous i.v. infusion (CIV), followed by a 4-day rest period, and then 1.6×10^6 IU/m²/day of maintenance IL-2 by CIV for 10 days. The maximum tolerated dose (MTD) of induction IL-2 was 9×10^6 IU/m²/day \times 4. In the phase II study, 52 patients received the MTD. Eighty percent of patients completed induction IL-2. Most patients exhibited some degree of capillary leak. One patient died of CMV pneumonia and one died of ARDS. Maintenance IL-2 was well tolerated. In the phase I/II study, 16 of 31 patients with non-Hodgkin lymphoma (NHL), 3/8 with Hodgkin disease (HD), 4/17 with AML, and 4/5 with ALL remain in CR. Two of six multiple myeloma (MM) patients remain in PR. Although the regimen of IL-2 identified had significant side-effects in some patients, it was well tolerated in the majority of patients. Phase III prospectively randomized clinical trials are in progress to determine if this IL-2 regimen will decrease the relapse rate after ASCT for AML and NHL.

Keywords: interleukin-2; autologous BMT; immunotherapy; PBSC

therapy. It is postulated that immunotherapy with interleukin-2 (IL-2), administered early after ASCT, at a time of minimal residual disease, may reduce the relapse rate.

An earlier phase I trial with IL-2 (Hoffman LaRoche, Nutley, NJ, USA) administered early after ABMT for hematologic malignancies identified a tolerable regimen which induced immunomodulatory effects.¹⁰ The encouraging clinical results observed in the course of that phase I trial^{11,12} stimulated the design of phase III trials. However, since Roche IL-2 became unavailable, the current phase I/II trial was performed to identify an equitoxic regimen of IL-2 provided by Chiron which could then be used in randomized trials to determine whether post-transplant IL-2 therapy will reduce relapses in patients with AML and NHL.

Materials and methods

Patient characteristics

Between November 1992 and April 1995, 67 patients with a median age of 44 (range 1-63) were treated with high-dose chemotherapy, with or without fractionated total body irradiation, plus an infusion of autologous stem cells from peripheral blood (PB; $n = 34$), bone marrow (BM; $n = 23$), or BM and PB ($n = 10$) followed by IL-2 therapy. Patients were treated at the University of Washington Medical Center, the Fred Hutchinson Cancer Research Center (FHCRC) or the Seattle Veteran's Administration Medical Center. Patients were treated for NHL (31), AML (17), Hodgkin's disease (HD; eight), MM (six), or acute lymphoblastic leukemia (ALL; four B cell, one T cell). Patient characteristics of the phase I and II components of the trial are summarized in Tables 1 and 2.

Eligibility criteria

Patients without progressive disease after ASCT were eligible to begin IL-2 therapy as soon as the following criteria were met: trilineage engraftment by bone marrow examination; neutrophil count $\geq 500/\text{mm}^3$; platelet count $\geq 20\,000/\text{mm}^3$ with ≤ 1 transfusion per day; creatinine < 2.0 mg/dl; bilirubin < 3.0 mg/dl; no active infection off antibiotics; > 7 days off treatment with corticosteroids, pentoxifylline or growth factors. Patients were ineligible if they had WHO grade III CNS, cardiac, pulmonary, hepatic or

The efficacy of autologous stem cell transplantation (ASCT) for advanced hematologic malignancies is limited by a high relapse rate.¹⁻⁴ In non-transplant settings, IL-2 has been reported to induce clinical responses in patients with acute myelogenous leukemia (AML),^{5,6} lymphoma,^{7,8} and multiple myeloma (MM)⁹ refractory to conventional

Table 1 Characteristics of patients in the phase I trial (*n* = 15)

	No. of patients
Age	15–63 (median 47)
Sex	6 M/9 F
Diagnosis	
NHL	7
MM	3
ALL	2
HD	2
AML	1
Conditioning regimen ^a	
A	6
B	4
C	3
D	2
Stem cell source	
BM	7
PB	5
BM/PB	3

^aRegimen A, cyclophosphamide (CY; 100 mg/kg), etoposide (VP-16; 60 mg/kg), TBI (12 Gy); regimen B, BCNU (300–600 mg/m²), CY (200 mg/m²), VP-16 (2400 mg/m²); regimen C, busulfan (BU; 14–16 mg/kg), CY (150–200 mg/kg); regimen D, BU (14 mg/kg), CY (60 mg/kg), modified TBI (9 Gy).¹³

renal toxicity. All protocols and consent forms were approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center or the University of Washington Medical Center.

Study design

Therapy with recombinant IL-2 (aldesleukin; Chiron Corporation, Emeryville, CA, USA) began a median of 46 (range 23–204) days after ASCT. Fifty-six of 67 patients (84%) began IL-2 therapy before day 100. In the phase I study, cohorts of three to four patients (total 15) received escalating dose levels of induction IL-2 consisting of 9, 10, or 12 × 10⁶ IU/m²/day by continuous i.v. (CIV) infusion for 4 or 5 days as inpatients (Table 3). After 4 days of rest, all patients received 1.6 × 10⁶ IU/m²/day of maintenance IL-2 by CIV infusion for 10 days via a portable infusion pump as outpatients. In the subsequent phase II study, 52 additional patients received the previously determined maximum tolerated dose (MTD) of induction IL-2, followed by the same maintenance IL-2 regimen.

Toxicity was graded according to WHO criteria. If a patient developed grade IV toxicity (or grade III neurologic or cardiac toxicity), IL-2 was stopped and not resumed. If a patient developed grade III toxicity (or grade II neurologic or cardiac toxicity), IL-2 therapy was discontinued until return to baseline or grade I toxicity at which time IL-2 therapy was resumed at 50% of the initial dose. If grade III toxicity recurred, IL-2 was stopped and not resumed. The MTD was defined as one dose level below the dose level at which three out of a maximum of six patients developed ≥grade III toxicity.

Supportive care

Acetaminophen, indomethacin, diphenhydramine, meperidine and furosemide were administered as clinically indicated. All but the first seven patients received prophylactic antibiotics – vancomycin and ciprofloxacin for adults, vancomycin and ceftazidime followed by a broad-spectrum oral antibacterial drug for children.

Immunologic studies

Immunophenotyping of peripheral blood mononuclear cells (PBMC) was performed by standard methods.¹⁶ The percentage of CD56 ‘bright’ and ‘dim’ cells was measured when the staining intensity led to clearly defined boundaries within the population of CD56⁺ PBMC. Lymphokine-activated killer effector (LAKe) activity was assessed by the ability of PBMC to lyse the natural killer (NK)-resistant Daudi cell line in a 4 h ⁵¹Cr-release assay without exposure to IL-2 *in vitro*.¹⁶ Significant LAKe activity was defined as >10% lysis at an effector to target cell ratio of 100:1.

Statistical analysis

Student’s *t*-test was used to compare hematologic parameters, LAKe activity, and absolute number and percentages of lymphocytes expressing particular phenotypic determinants as a function of IL-2 therapy. Statistics on relapse were calculated by the method of Kaplan and Meier.¹⁷

Results

Phase I study

Determination of the MTD: All 15 patients on the dose-escalation phase I portion of the study were evaluable for toxicity. Dose-limiting toxicities were seen in patients at induction levels II–IV. At induction level II, the highest daily dose level, dose-limiting toxicities were hallucinations in one patient, Gram-negative sepsis which was fatal in one patient 25 days after completion of IL-2 therapy, and non-fatal bacteremia in two other patients. None of the three infected patients had received prophylactic antibiotics. All subsequent patients received prophylactic antibiotics. At level III, dose limiting toxicities were stomatitis (one) and nausea with intractable hiccups (one). At level IV, three patients had dose-limiting toxicities. One patient, who had received BCNU as part of her conditioning regimen, developed fatal ARDS after maintenance IL-2. Autopsy showed diffuse alveolar damage that was attributed to BCNU. One patient was diagnosed with parainfluenza III virus pneumonia by bronchoalveolar lavage on day 3 of maintenance IL-2. IL-2 was stopped and the patient recovered. A third patient developed self-limited stomatitis. Level I was associated with no significant toxicities and was determined to be the MTD.

Clinical outcome: Of the seven patients with NHL, two patients treated at dose levels above the MTD died of the

Table 2 Characteristics and clinical outcomes of patients in the phase II trial

Diagnosis	Sex	Median age (range)	Stage at ASCT	Conditioning regimen ^a	Stem cell source		No. purged ^b	Relapse		In CR			
					PB ± BM	BM		No. patients	Median time (months)	Range (months)	No. patients	Median time (months)	Range (months)
NHL low grade (n = 11)	17M, 7F	46 (24–55)	3Rel1/CR2, 8 > CR2	A	7	4	3	4	7.5	6–13	7	20+	13+ to 37+
AML (n = 16)	7M, 9F	28 (1–59)	3 CR1	1C, 2F	2	1	—	1	9	—	2	—	12+, 25+
HD (n = 6)	5M, 1F	29 (14–44)	3 > CR2, 2 Rel1, 1 Ref	2A, 1B, 3E	4	2	—	4	11	2–22	2	—	18+, 20+
MM (n = 3)	3M	46 (45–50)	Stage III ^d	D	3	—	—	1	—	13	2 ^e	—	21+, 25+
ALL (n = 3)	3M	15 (9–38)	CR1	A	2	1	2	—	—	—	3	—	15+, 18+, 25+

ASCT = autologous stem cell transplant; Rel = relapse.

^aRegimen A, cyclophosphamide (CY; 100 mg/kg), etoposide (VP-16; 60 mg/kg), TBI (12 Gy); regimen B, BCNU (300–600 mg/m²), CY (200 mg/m²), VP-16 (2400 mg/m²); regimen C, busulfan (BU; 14–16 mg/kg), CY (150–200 mg/kg); regimen D, BU (14 mg/kg), CY (60 mg/kg), modified TBI (9 Gy);¹³ regimen E, BU (12 mg/kg), melphalan (100 mg/m²), thiotepa (500 mg/m²); regimen F, BU (14 mg/kg), CY (60 mg/kg), TBI (12 Gy).

^bNHL: purged with a panel of anti-B cell monoclonal antibodies and complement (C/Moab);¹⁴ AML: purged with 4-hydroperoxycyclophosphamide; ALL: one purged with C/Moab, one purged with VP-16.

^cTwo died during IL-2 treatment period, one died of cardiac arrest in CR.

^dDurie-Salmon classification.¹⁵

^eHad a PR after ASCT and have not progressed.

Table 3 Induction dose escalation scheme for the phase I trial

Level	n	Induction IL-2 dose
I	3	9 × 10 ⁶ IU/m ² /day × 4 days
II	4	12 × 10 ⁶ IU/m ² /day × 4 days
III	4	10 × 10 ⁶ IU/m ² /day × 5 days
IV	4	9 × 10 ⁶ IU/m ² /day × 5 days

toxicities cited above, three patients relapsed at 2, 5 and 21 months, and two patients (one with refractory low grade and one with intermediate grade in first relapse) remain in CR 38+ and 48+ months after ASCT. Of the two HD patients, one relapsed at 6 months, and one, transplanted in first relapse, is in CR at 39+ months. The one AML patient treated died in CR at 11 months due to pneumonia of unknown type. Of the two ALL patients, one relapsed at 3 months and one, who was in second CR at the time of ASCT, remains in CR at 39+ months. Of three patients with MM, one died of bacterial sepsis, and two who had a PR after ASCT progressed at 32 months and 41 months.

Phase II study

Clinical toxicity: Clinical toxicities of the 52 patients treated on the phase II portion of the study are summarized in Table 4. During induction IL-2, most patients had fever which lasted a median of 3 (range 1–6) days, and many patients exhibited some degree of capillary leak with mild weight gain in 50% of patients and with hypotension requiring fluids in 60%. However, three patients required pressors (for less than 24 h). A diffuse erythematous rash was noted in 40% of the patients, with desquamation in two patients. A worsening of pre-existing bronchiolitis obliterans organizing pneumonia (BOOP) occurred in one patient. Although all patients received prophylactic antibiotics, five developed bacteremia – four with coagulase-negative Staphylococcal species and one with JK diphtheroides – which resolved. Two AML patients died of pulmonary complications after completing induction IL-2: one patient with a prior history of HD treated with mantle radiation died of ARDS, and one died of CMV pneumonia 53 days after ASCT. The median length of stay in hospital for IL-2 therapy was 6 (range 2–37) days.

Ten patients received no maintenance therapy. Of these, five had had serious toxicity as described above (BOOP, ARDS, CMV pneumonia, desquamation, bacteremia), four refused and one was found to have CMV antigenemia and CMV in the urine from a sample collected prior to beginning induction IL-2. That patient completed induction IL-2, did not receive maintenance IL-2, received gancyclovir and never developed CMV disease.

Forty-two patients received maintenance therapy. The clinical toxicities observed are listed in Table 4. The most common symptoms were fatigue and malaise, which were cumulative and peaked toward the end of the maintenance infusion. Six patients developed hypotension with anorexia and responded to IV fluids. Fever ≥ grade 2 occurred in 10 patients. Four patients had bacteremia – three Gram-positive, and one, in a patient who had not received anti-

Table 4 Induction and maintenance IL-2 toxicities in the phase II trial

	Induction IL-2 (n = 52)	Maintenance IL-2 (n = 42)
Fever		
grade 1	1	9
grade 2	44	9
grade 3	5	1
Hypotension		
grade 1	10	8
grade 2	18	6
grade 3	6	0
Rash		
grade 1	19	0
grade 2	10	0
grade 3	2	0
Weight gain		
grade 1	21	6
grade 2	5	1
Non-infectious pulmonary toxicity		
grade 1	5	0
grade 2	5	0
grade 3	0	1
grade 4	1	0
Nausea		
grade 2	5	1
grade 3	3	3
Bacterial infection		
<i>C. difficile</i> diarrhea	2	0
bacteremia	5	4
Non-infectious diarrhea		
grade 2	3	0
grade 3	2	0
Viral infection		
oral HSV	2	1
fatal CMV pneumonia	1	0
Non-infectious stomatitis		
grade 2	1	0

biotics during the rest period, Gram-negative. Grade 3 pulmonary toxicity was seen in an infant with a history of intermittent collapse of the right upper lobe of the lung due to pre-transplant RSV bronchiolitis. She presented on the last day of maintenance IL-2 with tachypnea. This partially improved with oxygen and diuretic therapy, but definitive diagnosis of the pulmonary process was never made as she was found to have leukemic relapse in her bone marrow.

Dose delivery: Forty-one of the 52 patients (79%) received the complete IL-2 induction dose and 91% of the patients received ≥75% of the planned dose. Failure to receive the full IL-2 dose was due to refusal (three), capillary leak syndrome (three), hypotension (one), bacteremia (one), elevated aspartate aminotransferase (AST; one), BOOP (one) and pharmacy error (one).

Of the 42 patients who received maintenance IL-2, 28 (67%) received the full dose, 84% received ≥75% of the dose and 16% received <75% of the dose. Decreased dose delivery was due to refusal (three), nausea (two), bacteremia (three), fever (two), *C. difficile* diarrhea (one), anti-

biotic therapy for a prior bacteremia (one) and pharmacy error (one).

Hematologic effects: The hematologic effects of IL-2 therapy are shown in Figure 1. Lymphocyte, neutrophil and eosinophil counts rose during IL-2 therapy in the majority of patients. One patient developed transient unexplained neutropenia during maintenance IL-2 therapy. All patients developed thrombocytopenia during induction IL-2, with a nadir 24 h after finishing induction IL-2. The platelet count fell to $\leq 20\,000/\text{mm}^3$ in 21 patients whose median pre-IL-2 platelet count had been $40\,000/\text{mm}^3$ (range $17\,000\text{--}103\,000$). The remainder of the patients, whose median platelet count had been $118\,000/\text{mm}^3$ (range $49\,000\text{--}263\,000$), did not drop their platelet count below $20\,000/\text{mm}^3$. Platelet counts rose during maintenance IL-2 in all patients, and totally recovered by the end of maintenance therapy.

Other laboratory abnormalities: During induction IL-2, patients developed mild elevations in serum bilirubin (peak $0.2\text{--}6.0$ mg/dl, median 1.2) and creatinine (peak $0.5\text{--}3.6$ mg/dl, median 1.0). One patient developed an elevated AST (peak 780 mg/dl). The abnormalities were reversible in all patients and usually returned to baseline within 2–4 days after completing induction IL-2.

Immunomodulatory effects of dose level I: Lymphocytosis was observed after induction IL-2. It reflected a rise in the number of cells expressing CD3, CD4, CD8, CD56 and p75 (Figure 2). Cells expressing CD56, CD8 and p75 remained elevated at the end of maintenance therapy. The increase in CD56⁺ lymphocytes represented an expansion of both CD56 ‘bright’ and ‘dim’ cells (data not shown).

Before IL-2 therapy, cells from six of 22 patients exhibited mild LAK effector activity, with 10–19% lysis of Daudi. After induction IL-2, significant LAK effector activity was detected in PBMC from all 18 patients tested (without IL-2 *in vitro*), with a median of 35.6% lysis (range 11–98%; $P \geq 0.0005$ vs pre-IL-2 therapy). After maintenance IL-2, LAKe activity (82% lysis) was noted in cells from one of four patients tested.

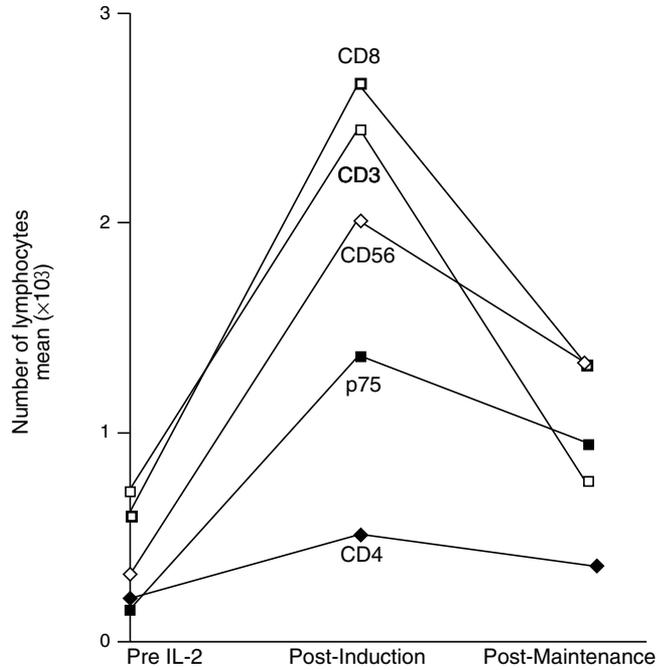


Figure 2 Effect of IL-2 therapy on the absolute number of lymphocytes expressing CD3, CD4, CD8, CD56 and p75. Values represent data from patients tested before IL-2, 24 h after induction IL-2, and 24 h after maintenance IL-2.

Patient outcome: The clinical outcomes for the phase II trial are summarized in Table 2. Fourteen of 24 NHL patients remain in CR a median of 20+ months (range 12+ to 37+) after ASCT. Of the six patients with HD, four relapsed while two remain in CR at 18+ and 20+ months.

Of the three patients with MM, one developed new bony lesions at 13 months and two, both with a PR after ASCT (defined as 75% or greater reduction in serum or urine monoclonal protein with absence of progression of bony disease), have not progressed at 21+ and 25+ months.

Of the 16 patients with AML, two died due to treatment, one died in CR 7 months after ASCT with idiopathic cardiac fibrosis, nine relapsed – including one who had relapsed cytogenetically before IL-2 therapy was initiated – and four remain in CR 12+ to 25+ months after ASCT. The three patients with ALL remain in CR at 15+ to 25+ months.

Discussion

Relapse remains the major limitation of ASCT for hematologic malignancy.^{1–4} Intensification of transplant conditioning regimens has not substantially reduced the problem.¹⁸ It is hypothesized that IL-2 administered early after transplantation might eradicate residual tumor cells, thereby reducing the relapse rate. The basis for this hypothesis is the following: (1) lymphocytes stimulated by IL-2 *in vitro* can lyse human hematologic malignant cells;¹⁹ (2) IL-2-responsive lymphocytes circulate early after ASCT;^{16,20} (3) IL-2 therapy is not cross-resistant with chemotherapy or radiotherapy; (4) IL-2 can induce objective clinical responses – including durable complete remissions – in

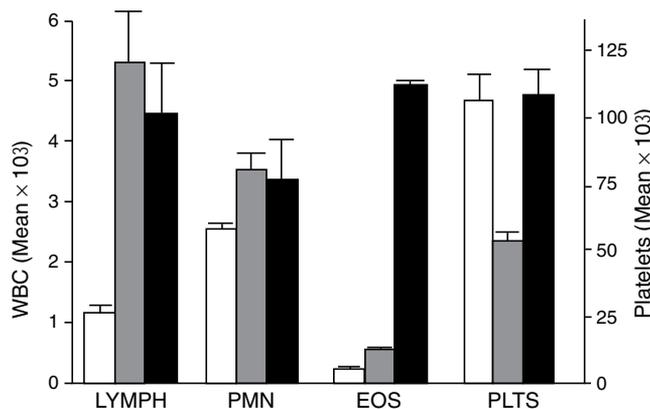


Figure 1 Blood counts as a function of IL-2 therapy after ASCT in the phase II trial. The mean \pm standard error of lymphocytes, neutrophils, eosinophils and platelets are displayed over time. Values represent data from patients tested before IL-2 (\square , $n = 50$); 24 h after induction IL-2 (\blacksquare , $n = 48$); and 24 h after maintenance IL-2 (\blacksquare , $n = 36$).

patients with AML, malignant lymphoma and multiple myeloma refractory to conventional therapy;^{5,6,8,9} (5) IL-2 is more likely to be effective against minimal residual disease, a setting which can be achieved by current transplant conditioning regimens; and (6) IL-2 after ASCT can induce a syndrome consistent with GVHD,²¹ and, therefore, might induce a GVL effect.

The IL-2 regimen tested in these trials evolved from our experience with solid tumor patients and from earlier studies with ABMT.^{11,12,22,23} Moderate doses of IL-2 were given to induce expansion of both T and non-T lymphocytes. A short rest period followed to allow recovery from IL-2 toxicities. A low dose of IL-2 was then administered to maintain the immunomodulatory effects. IL-2 therapy was begun early after recovery from the toxicities of ASCT, at a time of minimal residual disease and before relapses would be likely to occur.

The clinical toxicities of induction IL-2 observed in this study were similar to those previously described.^{10,24} In the phase I portion of the study, the main dose-limiting toxicities included pulmonary toxicity and bacterial infections (without prophylactic antibiotics). In the phase II trial with the MTD of IL-2, there were two unexpected deaths, while the toxicities were otherwise predictable and manageable. Side-effects of induction IL-2 consisted largely of fever and mild capillary leak. Laboratory abnormalities of liver and kidney function were mild, peaked at the end of induction IL-2, and quickly resolved. Lymphocytosis, neutrophilia, and eosinophilia were common. The latter two have been ascribed to the release of secondary cytokines including GM-CSF and IL-5.²⁵

There was a 6% mortality rate on this study, 3.5% at the MTD, due to infections and/or pulmonary toxicity. While all non-relapse causes of morbidity and mortality during or shortly after the IL-2 treatment are ascribed to IL-2, some may have been due to the transplant conditioning regimens and/or pre-existing medical conditions. The occurrence of CMV pneumonia in one of 67 patients treated with IL-2 is no different from the rate seen in non-IL-2-treated ASCT patients.^{26,27} A high incidence of bacterial infections, ascribed to an acquired defect in neutrophil chemotaxis in IL-2-treated patients,²⁸ has been reported in patients receiving IL-2 after BMT.²⁹ The serious bacterial infections in this study occurred largely in patients who had not received prophylactic antibiotics. The incidence of bacteremia was significantly reduced by prophylactic antibiotics (from 3/7 to 9/60 patients).

Four patients developed major non-infectious pulmonary toxicities. Although all four had a history of pulmonary insult – BCNU therapy, RUL collapse due to RSV bronchiolitis, BOOP and mantle radiation for HD – it is not known whether these predisposed or contributed to the toxicities attributed to IL-2.

Circulating IL-2-responsive cells that can mediate LAK activity *in vitro* are usually detectable as early as 2 weeks after ASCT.^{16,20,30} In the phase II trial, IL-2 induced a lymphocytosis which reflected an increase in cells of the cytotoxic T cell phenotype (CD8⁺) and of the activated NK phenotype (CD56⁺). Both CD56⁺ 'bright' cells, representing proliferating NK cells, and CD56⁺ 'dim' cells, representing cytotoxic NK cells,²⁵ increased in number dur-

ing IL-2 treatment, with a concurrent increase in the ability of the cells to kill NK-resistant tumor targets without exposure to IL-2 *in vitro*. Moreover, the percentage and absolute number of circulating lymphocytes which expressed p75 also increased significantly after IL-2 therapy. This β subunit of the IL-2 receptor binds IL-2 with intermediate affinity. NK cells constitutively express p75 and, therefore, can immediately respond to IL-2, whereas resting T cells do not express p75 but, after antigen recognition by the T cell receptor, the T cells express both CD25 and p75, and can respond to exogenous IL-2.³¹ The increase in cells expressing p75 is consistent with the increased number and proportion of NK cells and of activated T cells in the circulation after ASCT, capable of immediately responding to IL-2. The clinical significance of these immunomodulatory changes, which are consistent with those reported in other trials with moderate doses of IL-2,^{10,11,24} remains unknown.

The phase I and II trials were primarily designed to determine the MTD of this IL-2 regimen and to gain experience with its use, in anticipation of phase III trials.³² The phase II study involved a small and heterogeneous group of patients and, therefore, permitted no conclusions regarding clinical outcome.

Of the largest subgroup of patients in the phase II study, ie those with NHL, 58% remain in CR with a minimum follow-up of 1 year. These results are encouraging but not conclusive.

Of 16 patients treated for AML, there were two non-relapse deaths attributed to IL-2, nine relapses, and one death in CR, so that only four remain alive in CR. Overall, the relapse probability, 66%, is similar to that reported without IL-2⁴ and higher than that reported in our previous study with IL-2.^{11,33} However, the regimen and source of IL-2 used in this trial was different from that used in the past (Roche in the past, Chiron in the present trial), as was the stem cell source (only marrow in past trials vs largely PB or PB plus BM in the present trial). The possibility that relapses of AML might be more frequent after PBSC than after marrow transplant, as raised by some reports,^{34,35} might also explain the discrepant results. However, the patient groups in the various trials were small, heterogeneous, and not necessarily clinically comparable.

Our clinical results in a very small number of patients with HD, MM, and ALL, although encouraging, are necessarily uninterpretable. Although some promising results have been reported with IL-2 without ASCT in HD^{8,36} and in MM,⁹ one regimen of IL-2 given after ASCT for ALL in a randomized trial did not reduce the relapse rate.¹

The IL-2 regimen identified in the phase I trial and explored in the phase II trial is now being tested in two SWOG phase III trials of IL-2 after ASCT for AML and NHL. The results will determine whether consolidative immunotherapy with IL-2 administered after ASCT will decrease the relapse rates and improve disease-free and overall survival of such patients.

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