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Clinical report

Phase II evaluation of interleukin-4 in patients with non-Hodgkin's lymphoma: a Southwest Oncology Group Trial

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We performed a phase II, Southwest Oncology Group (SWOG) clinical trial of recombinant human interleukin-4 (rhuIL-4) in patients with previously treated non-Hodgkin's lymphoma (NHL). We studied 18 eligible patients with low-grade and 21 patients with intermediate- or high-grade NHL. All patients had received prior chemotherapy. A protocol amendment after the first four patients reduced the frequency of s.c. rhuIL-4 administration from daily to 3 times per week at 3 μg/kg and limited the number of prior chemotherapy regimens allowed. We documented no complete or partial responses in the low-grade NHL group [0%; 95% confidence interval (CI) 0–19%]. One patient in the intermediate/high-grade NHL group developed a partial response lasting longer than 15 months (5%; 95% CI 0–24%). Median survivals for the low- and intermediate/high-grade NHL groups were 15 and 13 months, respectively. Common toxicities included: arhralgia/myalgia, fatigue/malaise/lethargy, fever, headache, nausea and rigors/chills. Cardiac toxicity, gastrointestinal ulceration and nasal congestion due to rhuIL-4 were not prominent toxicities in our patients. Our previously treated NHL patients tolerated s.c. rhuIL-4 at a dose of 3 μg/kg given 3 times per week, but objective response rarely occurred. Further evaluation of rhuIL-4 in these patient populations does not appear warranted.

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Introduction

Interleukin (IL)-4 is a cytokine produced by activated T lymphocytes.[1] IL-4 exhibits pleiotropic biologic activities, and can potentially cause tumor regression via immunomodulation and/or direct anti-proliferative effects.

Biologic effects of IL-4 include: stimulating growth of B and T lymphocytes,[2] enhancing lymphokine-activated killer cell and cytotoxic T lymphocyte (CTL) activity, especially when combined with IL-2,[3,4,5] promoting growth of tumor-infiltrating lymphocytes,[6] and stimulating differentiation and proliferation of hematopoietic cells.[7]

Several reports suggested a rationale for using IL-4 as therapy for patients with lymphoid malignancies.[8] We previously showed that IL-4 inhibits the *in vitro* growth of 52 and 60% of fresh human multiple myeloma and lymphoma specimens, respectively.[9] DeFrance *et al.* reported IL-4 inhibits proliferation of freshly isolated tumor specimens from patients with low- or intermediate-grade non-Hodkin's B cell lymphoma (NHL).[10] Luo *et al.* reported IL-4 inhibits *in vitro* proliferation of B cell chronic lymphocytic leukemia cells.[11]

In vivo models confirmed IL-4 anti-tumor activity against lymphoid tumors. Santra and Ghosh reported IL-4 helps maintain CTL activity in a murine B cell lymphoma model.[12] IL-4 impedes dissemination of human B cell lymphoma cells (Daudi) in severe combined immune deficient (SCID) mice.[13] Of note, IL-4 does not alter the growth of Daudi cells *in vitro*,

suggesting the *in vivo* results do not involve a direct effect on proliferation.

IL-4 also modulates expression of HLA class I, II and cell adhesion molecules.[14–16] These molecules are relevant to lymphoma immunosurveillance and tumorigenicity, and have particular clinical relevance because large cell lymphoma patients whose tumors lack expression of HLA-DR have much poorer survival after treatment with chemotherapy.[17]

We now report the results of a Southwest Oncology Group (SWOG) phase II clinical trial of recombinant human (rhu) IL-4 in patients with low- or intermediate/high-grade NHL whose tumors progressed following previous treatment with curative intent.

Materials and methods

Eligibility criteria

Protocol entry required a biopsy proven diagnosis of low-, intermediate- or high-grade malignant NHL, including transformed lymphomas. Patients with lymphoblastic lymphoma were not eligible. The original protocol version required three prior chemotherapy regimens in patients with low-grade NHL and two prior chemotherapy regimens in patients with intermediate/high-grade NHL. A subsequent protocol amendment, intended to enroll patients with less prior therapy, required at least one and no more than three prior chemotherapy regimens in patients with low-grade NHL, and at least one and no more than two prior chemotherapy regimens in patients with intermediate/high-grade NHL. Patients previously treated with high-dose chemotherapy and autologous marrow or peripheral blood stem cell transplantation were eligible for study entry. For these patients, the salvage chemotherapy used to determine responsiveness prior to transplant and the subsequent high-dose chemotherapy counted as one regimen.

Other protocol entry requirements included: bidimensionally measurable disease, performance status 0–2 according to SWOG criteria, absolute granulocyte count $\geqslant 1500$ μl beyond the nadir from previous chemotherapy, hemoglobin $\geqslant 9$ g/dl (transfusion allowed), platelet count $\geqslant$ institutional lower limits of normal, bilirubin $\leqslant 1.5$ times institutional upper limit of normal, creatinine $\leqslant 2\times$ institutional upper limit of normal, and estimated or measured creatinine clearance $\geqslant 60$ cm^3/min.

Exclusion criteria included: known human immunodeficiency virus (HIV) infection; pregnant or nursing women; prior malignancy (except for adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer or other cancer with disease free interval 5 years or longer); central nervous system involvement; history of impaired cardiac status; abnormal pretreatment gated cardiac radionuclide scan (MUGA scan) or echocardiogram; patients receiving digitalis preparations, steroids, antiarrhythmics, β-blockers or calmodulin inhibitors; prophylactic or preventive use of granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor; significant arrhythmias on pretreatment electrocardiogram (EKG); moderate to severe compromised pulmonary function; peptic ulcer disease (history or current); and inability to discontinue antihypertensive medications.

The study protocol was reviewed and approved by the Human Subjects Institutional Review Boards of all participating institutions. All patients were informed of the investigational nature of the study and gave written informed consent in accordance with institutional and federal guidelines.

Drug administration

The National Cancer Institute (NCI) and Schering-Plough Pharmaceuticals supplied rhuIL-4 (NSC-618085, IND-4348) for use in this study. Vials containing 480 μg of sterile, lyophilized rhuIL-4 were reconstituted with sterile water for Injection, stored at 2–8°C and used within 8 h. Patients received rhuIL-4 by s.c. injection. Patients were observed in a medical facility for at least 2 h after the first two doses of rhuIL-4. If no significant acute side effects occurred, the patient or a family member administered subsequent injections at home, usually at bedtime. Prophylactic medications included acetaminophen 650 mg orally 1 h before and 3 h after rhuIL-4 injection, and sucralfate 1 g orally 4 times daily on the days of rhuIL-4 administration.

The first four patients entered on this study received rhuIL-4 at a dose of 3 μg/kg daily. Toxicities encountered by these four patients led to a temporary study closure. Extensive review determined that the toxic effects in these initial patients most likely occurred due to extensive disease therapy prior to treatment with rhuIL-4 and to progressive disease while on treatment with rhuIL-4. A subsequent protocol amendment changed the rhuIL-4 schedule to 3 μg/kg 3 times weekly and changed the number of previous chemotherapy regimens allowed (see Eligibility criteria, above). This amended schedule and entry criteria continued for the remainder of the study. Patients continued treatment with rhuIL-4 until they developed disease progression, delay of treatment >2 weeks, unacceptable toxicity or the patient desired to stop treatment.

Dose modifications

We utilized aggressive supportive care measures to keep preventable toxicities from becoming severe enough to warrant dose reduction. The protocol recommended the following treatments for the associated symptoms: acetaminophen or ibuprofen for chills and fever; acetaminophen or hydromorphone for headache; pseudoephedrine for nasal stuffiness; prochlorperazine or lorazepam for nausea/vomiting; and diphenoxylate for diarrhea.

Full dose treatment continued despite grade 0–2 SWOG criteria toxicity, except for grade 2 hemorrhage, cardiac or neurotoxicity. Grade 2 hemorrhage, cardiac or neurotoxicity and all other grade 3 or 4 toxicities (with the exception of bilirubin where only grade 4 toxicity was considered dose limiting or 10-fold evaluation of liver enzymes over pre-study value) required treatment be held. Treatment resumed with a 50% dose reduction (1.5 μg/kg) after the dose-limiting toxicity returned to grade 1 or less. Subsequent dose-limiting toxicity required an additional dose reduction to 0.75 μg/kg. Only two dose reductions were allowed.

Efficacy and safety evaluation

Bone marrow aspirate and biopsy were required within 42 days prior to study registration. This requirement was waived for patients with a positive bone marrow study within the previous 6 months if they received no therapy since the prior biopsy. Complete blood count (CBC), platelets, creatinine, bilirubin, SGOT, sodium, potassium, CO_2, chloride and LDH were evaluated pre-study, repeated weekly for the first 6 weeks on study, and then on weeks 9, 11, 14, 16, 19 and/or at the off-study evaluation. MUGA scan or echocardiogram were obtained pre-study, and repeated on weeks 4, 9, 14, 19 and/or at the off-study evaluation. Chest X-ray, CT scans of the abdomen and pelvis, and other scans as clinically indicated for tumor documentation were obtained pre-study and repeated at week 9 and/or during the off-study evaluation.

Statistical considerations

Patients were stratified into two disease categories of NHL patients (low grade and intermediate/high grade). Patients within each stratum were accrued according to a two-stage design with response as the primary end point. The previously reported SWOG response criteria were used.[18] A response probability of 40% or greater would be of interest for further exploration of rhuIL-4 in either disease category, while further testing would not be pursued if the response probability was 20% or lower. We planned to initially enroll 25 patients in each disease category and if four or fewer of the first 25 patients responded to treatment, close the study for that disease category. If at least five responses occurred, 20 additional patients would be enrolled. Fifteen or more responses out of 45 would be considered evidence warranting further study of this regimen provided other factors such as toxicity and survival also appeared favorable. The planned design has a significance level of 0.052 and a power of approximately 0.9. Accrual to the study occurred over approximately 5 years. The study was terminated before the first-stage accrual goals were met due to lack of further availability of rhuIL-4.

Results

Forty-one patients with NHL were registered to the study between August 1994 and November 1999 including 19 patients with low-grade NHL and 22 patients with intermediate/high-grade NHL. One patient with low-grade lymphoma was ineligible because of inadequate pre-study documentation and one intermediate/high-grade patient did not have bi-dimen-

Table 1. Patient characteristics

	Low-grade NHL (n=18)	Intermediate/high-grade NHL (n=21)
Age (years)		
median	61.0	65.0
minimum	38	28
maximum	73	82
Sex		
male	10 (56%)	14 (67%)
female	8 (44%)	7 (33%)
Race		
white (non-Hispanic)	16 (89%)	17 (81%)
black (non-Hispanic)	1 (6%)	2 (10%)
Hispanic	1 (6%)	2 (10%)
Performance status		
0	15 (83%)	12 (57%)
1 or 2	3 (17%)	9 (43%)
No. of prior chemotherapy regimens		
1	7 (39%)	10 (48%)
2	5 (28%)	11 (52%)
3	6 (33%)	
Extranodal disease sites		
bone marrow	9	4
gastrointestinal	0	1
kidney	1	1
liver	3	1
lung/pleura	1	6
skin	0	1

sionally measurable disease. Table 1 shows the clinical characteristics of the low- and intermediate/high-grade NHL patients. Patient age extended up to 82 years old. The proportion of males and females was approximately equal in the low-grade NHL group, while the intermediate/high-grade group contained a preponderance of males. The majority of the patients in both of the disease categories were white (non-Hispanic) with SWOG performance status 0. Patients in the low-grade NHL group received more prior chemotherapy (33% received three prior regimens) than the intermediate/high-grade NHL group as expected by the eligibility criteria. Other than lymph nodes, the low-grade lymphomas most commonly involved bone marrow and the intermediate/high-grade lymphomas most commonly involved lung/pleura.

We observed no complete responses in either disease group [95% confidence interval (CI) 0–19%] (Table 2). One patient (5%) in the intermediate/high-grade NHL group developed a partial response (95% CI 0–24%). Stable disease/no response occurred in one-third or fewer of patients in either category and the majority of patients in both disease categories displayed evidence of increasing disease. Patients in the low-grade and intermediate/high-grade NHL groups displayed median survival times of 15 and 13 months, respectively (Figure 1).

Table 2. Objective responses

	Low-grade NHL	Intermediate/ high-grade NHL
Complete response	0 (0%)	0 (0%)
Partial response	0 (0%)	1 (5%)
Stable/no response	4 (22%)	7 (33%)
Increasing disease	13 (72%)	13 (62%)
Assessment inadequate	1 (6%)	
Total	18 (100%)	21 (100%)

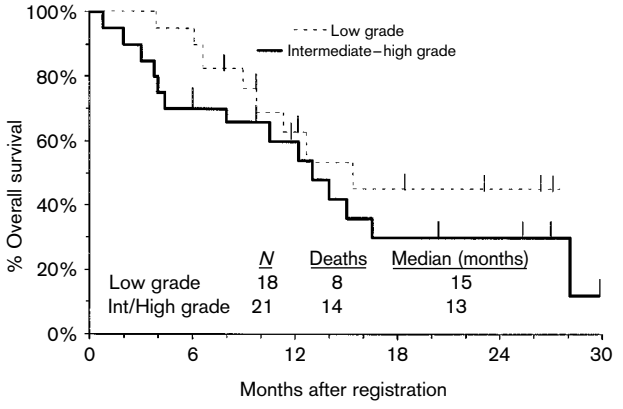

Figure 1. Overall survival of patients with low- or intermediate/high-grade NHL treated with rhuIL-4.

The responding patient is a 57-year-old female with a diagnosis of follicular mixed and diffuse large, B cell malignant lymphoma. She developed a partial response to initial CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, Prednisone) and proceeded to complete remission following high-dose chemotherapy and autologous stem cell transplantation. Within 5 months of high-dose chemotherapy and transplantation, she developed disease progression and was treated with rhuIL-4. Pre-study disease sites included para-aortic and mesenteric adenopathy measurable by CT scan. Partial remission was documented after approximately 4 months of rhuIL-4 therapy. She continued on rhuIL-4 for a total of 14 months, until study drug was no longer available. At the time of most recent follow up, she remained in remission, off therapy for approximately 5.5 months.

Toxicities encountered by the first four patients who received rhuIL-4 at 3 μg/kg/day included: Patient 1, eosinophilia, pleural effusion associated with progressive lymphoma; Patient 2, headache, fatigue, bowel perforation associated with progression of lymphoma in the bowel; Patient 3, slight decrease in cardiac ejection fraction by echocardiography, increasing lower extremity edema, enlarged heart on chest X-ray, but no symptoms or physical examination findings indicting congestive heart failure; Patient 4, increasing lower extremity edema progressing to anasarca, prerenal azotemia and no changes in cardiac ejection fraction. After extensive review of these patients and consultation with the NCI's Cancer Therapy Evaluation Program (CTEP), we concluded that these toxicities were due to a combination of rhuIL-4 therapy, extensive therapy prior to rhuIL-4 and progression of lymphoma.

We observed acceptable rhuIL-4 toxicities following the protocol amendments to change the schedule to 3 μg/kg 3 times per week and limit the number of previous chemotherapy regimens. Toxicities did not differ according to disease category (low- versus intermediate/high-grade). Table 3 shows the frequency and grade of toxicities for the combined patient groups. Common low-grade toxicities included arthralgia/myalgia, fatigue/malaise/lethargy, fever, headache, nausea and rigors/chills. The changes in cardiac ejection fraction were minimal and likely within the limits of variation of the studies (MUGA or echocardiogram) from test to test. Other than occasional lower extremity edema, the ejection fraction changes were not associated with clinical signs or symptoms indicating congestive heart failure.

Table 3. rhuIL-4 toxicities in patients with low- or intermediate/high-grade NHL

Toxicity	No. of patients with toxicity ($n=39$)			
	Grade 1	Grade 2	Grade 3	Grade 4
Alkaline phosphatase increase	3	0	1	0
Anemia	2	3	0	0
Arthralgia	0	2	0	0
Bilirubin increase	0	3	0	0
Confusion	1	2	0	0
Constipation/bowel obstruction	0	0	2	0
Creatinine increase	5	1	1	0
Diarrhea	2	1	0	0
Dizziness/vertigo	0	2	0	1
Dyspnea	0	4	1	0
Edema	4	2	3	1
Fatigue/malaise/lethargy	11	6	3	0
Fever	7	4	0	0
Gastritis/ulcer/bowel perforation	2	0	0	1
Headache	6	9	1	0
Hypertension	0	1	3	0
Hypotension	1	0	2	0
Ejection fraction decrease/CHF	5	1	0	0
Leukopenia	3	3	0	0
Myalgia/arthralgia	10	1	0	0
Nausea	10	2	1	0
Pruritus	1	0	1	0
Renal failure	0	0	0	1
Rigors/chills	9	2	0	0
SGOT increase	4	1	0	0
Thrombocytopenia	0	1	1	0
Vomiting	5	3	0	0
Weight gain	3	0	1	0

The most common grade 3 toxicities due to rhuIL-4 included hyper- or hypotension, edema, weight gain; fatigue/malaise/lethargy and nausea. The grade 4 renal failure occurred in a patient (Patient 4 mentioned above) with progressive retroperitoneal adenopathy with obstructive anasarca and was unlikely related to rhuIL-4. The grade 4 bowel perforation occurred in Patient 2 mentioned above who had pathologic documentation of lymphoma in the bowel.

Discussion

In previous phase II studies rhuIL-4 resulted in occasional anti-tumor activity against metastatic malignant melanoma and non-small cell lung cancer. Margolin *et al.* evaluated i.v. rhuIL-4 and reported one complete response of above 30 months duration out of 30 patients with metastatic melanoma, but they saw no responses in 19 patients with advanced renal cancer.[19] Vokes *et al.* studied rhuIL-4 given as a 3 times per week s.c. injection at 0.25 or 1.0 μg/kg in 63 patients with advanced non-small cell lung cancer.[20] They observed one partial response of above 5.5 years duration in the 1.0 μg/kg group. Similar to these reports, we observed rare, but one relatively long-lived objective response in our group of NHL patients.

A summary of previous phase I and II clinical trials evaluating rhuIL-4 given as a s.c. injection or intermittent i.v. infusion indicated that s.c. doses up to 5 μg/kg/day or 10 μg/kg given 3 times per week were safe and reasonably well tolerated.[21] The group of lymphoma patients in our study tolerated rhuIL-4 at 3 μg/kg s.c. 3 times per week, but not 3 μg/kg given daily. The difference in dose tolerance is likely due extensive prior therapy in our lymphoma patients. Many more active treatment regimens, including high-dose chemotherapy and transplantation, are available for lymphoma patients, while the melanoma and renal cell carcinoma patients studied in previous rhuIL-4 trials had fewer previous treatment options.

Similar to previous trials, the most common rhuIL-4 toxicities we observed included arthralgia/myalgia, fatigue/malaise/lethargy, fever, headache, nausea and rigors/chills. Preclinical toxicology studies suggested the possibility of IL-4-induced cardiac toxicity.[21] We followed our patients closely by electrocardiograms and with MUGA scans or echocardiograms. We saw

minor changes in left ventricular ejection fraction, but these were not severe enough to likely result in congestive heart failure. We feel the lower extremity edema in our study occurred as an independent toxicity from rhuIL-4, not directly related to left ventricular function. Previous clinical studies of rhuIL-4 reported frequent nasal congestion[19] and acute gastric mucosal injury with occasional ulceration.[22,20] They were not prominent in our study, perhaps due to liberal use of pseudoephedrine and sucralfate, respectively. The one episode of bowel perforation in our study occurred in a patient with pathologic documentation of lymphoma in the same area of bowel.

Conclusions

Previously treated NHL patients tolerate s.c. rhuIL-4 at a dose of 3 μg/kg given 3 times per week, but objective anti-tumor response is rare. We conclude that further evaluation of rhuIL-4 in this patient population does not appear warranted.

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