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PHASE II STUDY OF INTERLEUKIN-4 IN INDOLENT B-CELL NON-HODGKIN'S LYMPHOMA AND B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA: A STUDY OF THE EASTERN COOPERATIVE ONCOLOGY GROUP (E5Y92)

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Summary

Recombinant IL-4, 5µg/kg thrice weekly for 3 weeks followed by a 2-week rest period (one cycle) was administered to 32 eligible previously treated B-CLL (7 patients) or low-grade B-cell lymphoma patients (25 patients). Two cycles were given before response was evaluated. IL-6 serum levels were evaluated prior to therapy in all patients and at 12 weeks on study in 7 patients. No CLL patients responded. A partial response was observed in 3 lymphoma patients of 1.2, 3.0 and 3.5 months' duration and stable disease (median 1.5 months) was observed in another 7 lymphoma patients. The median survival from registration on study was 29.7 months with 7 patients alive at the time of analysis for a median follow-up of 72.8 months. Toxicity was generally mild with no grade 4 non-hematologic toxicity observed. Recombinant IL-4 treatment was well tolerated in this study but had minimal anti-tumor activity.

Keywords

interleukin-4; interleukin-6; low-grade lymphoma; chronic lymphocytic leukemia

Interleukin-4 (IL4), a 20 kilodalton 129 amino acid lymphokine, inhibits DNA synthesis in B-cells and suppresses the autocrine proliferation of B-cells. Furthermore, IL4 blocks the progression of B-cells in or into the G1 stage of the cell cycle (1). Interleukin-6 (IL6), a growth factor for B-cells, is downregulated by IL-4 (2), and IL-4 inhibits IL6 secretion by activated monocytes (3). A decrease in malignant lymphocytes and increased hemoglobin concentration and platelet count have been observed in some CLL patients in early phase I–II studies of IL-4(4–6).

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We previously performed a phase I–II study of Sterling recombinant IL-4 given intravenously 5 days per week for 3 weeks followed by a two-week break and then a repeat course in patients with indolent lymphoma or chronic lymphocytic leukemia (CLL). Three patients were treated at a dose of 250 $\mu\text{g}/\text{m}^2$ and one at a dose of 375 $\mu\text{g}/\text{m}^2$. Two of those patients, one with CLL and one with low-grade lymphoma, had a partial response, another low-grade lymphoma patient had stable disease for 16 weeks and another had a minor response. This study was terminated early after 4 patients were enrolled when Sterling IL-4 was withdrawn and no longer available. However, these responses led to initiation of this ECOG study with Schering IL-4.

Toxicity reported with IL-4 includes constitutional symptoms, elevated liver function tests and weight gain secondary to fluid retention. Animal studies suggest that cardiac toxicity may be caused by IL-4 administration, and clinical cardiac toxicity may have been observed (4).

Clinical pharmacokinetic studies have detected IL4 in serum up to 8 hours after a subcutaneous injection, in contrast to rapid clearance after intravenous administration (5–8). Consequently, subcutaneous administration was employed in the present study.

PATIENTS AND METHODS

The primary objectives of the study were to evaluate response rates to recombinant human IL4 in patients with previously treated low-grade B-cell lymphoma or B-CLL, and to evaluate the toxicity of the regimen employed.

This study was initiated in December, 1994 with a Simon 2 stage design. It was suspended from December, 1995 until January, 1997 to assess the results of stage I and finally closed when accrual goals were met in July, 1998.

Patients

A histologically confirmed diagnosis of measureable indolent B-cell lymphoma (A–C or E of the Working Formulation, or B-CLL) was required in order to be eligible for the study. Patients were required to be at least 16 years of age and to have progressive previously treated disease. Prior chemotherapy, radiation therapy and biological therapy must have been completed at least 4 weeks prior to entry on study. No more than 2 prior chemotherapy regimens or one prior biologic response modifier regimen were allowed, and concurrent radiation therapy was disallowed as well. Autoimmune thrombocytopenia or hemolytic anemia excluded patients from the study, as did HIV or any other significant infection, or peptic ulcer disease. Patients were required to have no other significant illness or an organ allograft, and patients with previous or current brain metastases were not eligible. Patients with asthma or other breathing disorder, seizure, atopic dermatitis, ascites or pleural effusions were ineligible, as were patients with a history of an additional neoplasm other than skin cancer or curatively treated carcinoma in situ of the uterine cervix within 5 years. Eligible patients were required to be ambulatory with an ECOG performance status of 0 or 1 and to have an estimated survival expectancy of at least 4 months. Treatment with folate antagonists, steroids (including topical), non-steroidal anti-inflammatory agents, anticoagulants, radiation therapy, chemotherapy or other cancer treatments were not allowed during the study.

Patients were required to have a white blood cell count $>3,500/\mu\text{L}$ and platelet count $>50,000/\mu\text{L}$ at the time of registration on study as well as a serum total bilirubin $<3\times$ the upper limit of normal and a serum creatinine concentration $<2\times$ the upper limit of normal. A baseline MUGA scan was required prior to study to demonstrate normal left ventricular

function, and before the third cycle of treatment, and then monthly while on study. An electrocardiogram was also done prior to study and monthly thereafter while on study. Women of child-bearing age were required to have a negative pregnancy test and to be non-lactating. Patients were instructed to practice contraception. All participants gave written informed consent prior to registration, and the study was approved by the institutional review boards of participating institutions. Eligibility, registration on study, and pathology were confirmed centrally.

Treatment

Each treatment cycle consisted of subcutaneously administered recombinant IL4 (supplied by Schering Corporation), 5 µg/kg (actual body weight) thrice weekly for 3 weeks, followed by a 2 week rest period. All treatments were outpatient. Two cycles of treatment were given and response was then evaluated. The first week of treatment was given by a clinical oncology nurse and, if no injection-related toxicity occurred within 3 hours of observation, subsequent doses were administered by the patient or family member at home after appropriate instruction. The patient was seen weekly throughout the study, however. All adverse reactions were reported centrally and graded according to the ECOG Common Toxicity Criteria of 1992.

If grade 2 cardiac or neurologic toxicity or bleeding was observed with treatment, treatment was to be discontinued and resumed when the toxicity was resolved, at 50% of the original dose and continued at that dose for the rest of the study. A permanent 50% dose reduction was also required for grade 3 or 4 nausea, vomiting, diarrhea, fever or hematologic toxicity. Grade 3 cardiac or neurological toxicity required that the patient be taken off study, as did any grade 4 toxicity other than hematologic.

Acetaminophen and cimetidine were administered orally during treatment at standard doses and schedules. Anti-emetics and anti-diarrheal agents were administered as required. Diphenhydramine or hydroxyzine hydrochloride were administered if required for erythema or pruritus.

Patients were evaluated for response after completion of treatment cycle 2 (week 10) according to the ECOG Response Criteria for lymphoma and CLL, which were included in the protocol but not formally published elsewhere. Briefly, lymphoma patients with a 50% or greater (but < 100%) reduction in the sum of the products of the dimensions of measurable disease for at least 4 weeks without the appearance of new lesions were considered to be partial responders, and stable disease was defined as no change in measurable disease for at least 4 weeks in the absence of new lesions. Complete response was defined as the absence of any evidence of disease. For patients with CLL, a partial response was defined as at least a 50% reduction in peripheral lymphocyte count, lymphadenopathy and hepatosplenomegaly as well as one or more of the following: 50% improvement over baseline of the granulocyte count, platelet count or hemoglobin concentration if impaired prior to treatment. Complete response designation required absence of lymphadenopathy and hepatosplenomegaly as well as a normal complete blood count and marrow aspiration. Patients with a complete (CR) or partial response (PR), or stable disease then began cycle 3. Patients with progressive disease at any time during the study were taken off study. Patients with CR or PR after cycle 3 continued on study until disease progression was documented. Patients with stable disease after cycle 3 were taken off study.

Ancillary Studies

All enrolled patients were to have blood interleukin-6 levels determined prior to treatment and at 12 weeks on study (Philip R. Greipp, M.D.), and CLL patients had immunophenotyping performed on their leukemic cells prior to treatment (Elisabeth Paietta, PhD).

Statistical Methods

The accrual goal for this study was 33 evaluable patients. Further study of this agent was deemed appropriate if at least a 20% response rate (CR + PR) was observed in the present study. It was planned to terminate the study if no CRs were observed within 12 weeks of treatment in the first 15 patients. It was calculated that the overall probability of rejecting IL4 as active if it has a true response rate of 20% is 0.098, and the overall probability of rejecting it as active if it has a true response rate of 5% is 0.924. With 33 patients, the 90% confidence interval for the true response rate is no wider than 31%.

RESULTS

A total of 37 patients (9 with B-CLL and 28 with low-grade B-cell lymphoma) were entered on the study. Three lymphoma patients and 2 CLL patients were ineligible for various reasons (2 no data received, 1 had more than 2 prior treatment regimens, 2 had intermediate grade histology on central pathology review); therefore 32 patients (25 with low-grade lymphoma and 7 with CLL) were eligible and evaluable for response. All patients who received any IL4 were evaluated for toxicity. Characteristics of eligible patients at study entry are shown in Table 1. A partial response of short duration (3.5, 3.0, and 1.2 months) was achieved in 3 male lymphoma patients. Stable disease was observed in another 7 patients for a median of 1.5 months and 22 patients progressed on therapy. The response rate was 9.4% for all eligible patients and the corresponding 90% C.I. adjusted for the two-stage design using the method of Atkinson and Brown (9) was (2.7%; 23.4%). The response rate was 12.0% with 90% C.I. (2.5%; 31.2%) for all eligible low-grade lymphoma patients. None of the CLL patients responded with at least a PR. The median survival of the 32 eligible patients from registration to death or date last known to be alive was 29.7 months, with 95% C.I. (11.9,45.0 months). Seven patients were alive at the time of this analysis with a median follow-up of 72.8 months.

Toxicity of subcutaneous IL-4 was generally mild in this study (Table 3). There were no non-hematologic grade 4 toxicities. One patient had severe hyponatremia of unknown etiology on study, but this continued after he was taken off study until he died 7 months later and was not considered IL4-related. Grade 1–2 cardiac toxicity was noted in 6 patients, but none required treatment interruption or dosage reduction. Grade 3 toxicities were primarily hematologic and neurologic. Four of the grade 3 neurologic toxicities were fatigue and one was dizziness. The 5 patients with grade 3 neurologic toxicity were taken off study after one course of treatment. Patients with grade 3–4 hematologic toxicity were subsequently treated with half-dose IL-4 on the same schedule. Two grade 3 toxicities classified as “Other” in Table 2 were described as “anxiety” and “muddled thinking.”

IL6 blood levels were determined in 21 eligible patients prior to therapy and 7 of those had repeat determinations after 12 weeks on study. The median IL6 baseline level was 7.5 units with a wide range of 4.7 – 170.1 units. For the 7 patients who had both samples drawn (two with stable disease and 5 who progressed) the median difference between the 2 samples was 0.7 units (range, –4.7 – 4.6 units), and the sign rank test indicates no significant difference between the before and after treatment samples. Therefore, IL4 administration in this study did not reduce blood IL6 concentration in the 7 patients studied.

DISCUSSION

The rationale for bringing IL-4 to clinical trial has been extensively discussed in the literature (1–3,6,8,10–12). The dose and schedule of IL-4 used in this study are similar to those used in other phase II studies. Gillece et al (13) reported dose limiting toxicity at 5 µg/kg daily, subcutaneously. Leach et al (14) reported that 5 µg/kg/day subcutaneously was well tolerated when administered thrice weekly. Taylor et al (15) in a more recent study reduced the frequency of IL-4 administration from daily to thrice weekly due to toxicity from the daily schedule, which confirms our choice of a thrice weekly schedule. Despite theoretical reasons for optimism, the results of subcutaneous IL-4 administration to previously treated low-grade lymphoma and CLL patients in this study are disappointing. Other trials have been disappointing as well. Prendiville, et al (16) reported only transient minor responses in 2 patients with lymphoma enrolled in a phase I trial. Interestingly, they also observed transient progression in a lymphoma patient under treatment in that study. We previously reported a patient with B-CLL who had a complete response to IL-4 but developed multiple myeloma on treatment (17).

Taylor, et al (15) treated 18 low-grade and 21 intermediate- or high-grade lymphoma patients with subcutaneous IL-4 thrice weekly at a dose of 3µg/kg/dose and observed a PR in only one patient (intermediate-/high-grade group). That PR was durable, however, lasting 15+ months. As in our study, IL-4 was generally well tolerated on that schedule.

Lundin, et al (18) treated 14 patients with B-CLL in partial remission after chemotherapy with 1–3 8-week cycles of escalating doses of subcutaneous IL-4 (2, 4 or 6µg/kg/dose) for 3 days per week. Ten of the patients progressed on study, but 1 of 13 patients with lymphadenopathy had a reduction in nodal disease >50% and 4 additional patients had 50% or less reduction in measureable lymphadenopathy. Again, IL-4 treatment was well tolerated.

Kurtz, et al (19) observed a 13% response rate (1 CR and 4 PR) in 39 patients with relapsed or refractory indolent or aggressive lymphoma treated with IL-4 2.5 or 5.0 µg/kg subcutaneously for 28 days of a 42 day cycle. All responders were treated at the 5.0 µg/kg dose level. The median duration of response was 8.3 months. Frequent grade 3–4 toxicity complicated this rather intense dosing schedule, however.

The 12% PR rate in lymphoma patients in the present study is comparable to the results reported by Kurtz, et al (19). However, our schedule of thrice weekly every other day administration appears to be considerably less toxic.

Although studies to date with recombinant human IL-4 in B-cell neoplasms have been disappointing, it is clear from the data cited above that some patients with B-cell neoplasms obtain therapeutic benefit from its administration. Whether the agent should be studied further in earlier patients and/or in combination with other agents or more intensive schedules and doses should be discussed (20) in the context of the availability of new, highly active agents for these diseases such as rituximab, bendamustine and lenalidomide.

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TABLE 1

Study Characteristics of 32 Eligible Patients

	N	%
Sex		
Male	23	71.9
Female	9	28.1
Race		
White	31	96.9
Black	1	3.1
Age, years		
Median	61	
Range	41–76	
Hemoglobin, g/dL		
Median	13.2	
Range	7.9–17.3	
Platelets, $\times 10^3/\mu\text{L}$		
Median	156	
Range	55–399	
WBC, $\times 10^3/\mu\text{L}$		
Median	64	
Range	19.4–386	
NHL	25	78.1
Stage III/IV	8/17	
Histology A/B	7/12	
C,D/E 3/3		
Prior Rx; None	5	
1	12	
2	8	
CLL	7	21.9
Rai stage		
II	1	
III	3	
IV	3	
Prior Rx: None	3	
1	2	
2	2	

CLL indicates chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; WBC, white blood cell.

TABLE 2

Interleukin-4 Toxicity in 37 Registered Patients

Toxicity	Grade		
	1,2	3	4
Granulocytopenia	6	2	1
Thrombocytopenia	10	2	1
Anemia	15	3	
Bleeding	1		
Infection	6	1	
Fever without infection	18	1	
Genitourinary	11		
Nausea	10		
Vomiting	5		
Diarrhea	7		
Stomatitis	1		
Hepatic	23		
Pulmonary	8	1	
Cardiac	6		
Hypertension	1		
Skin	6		
Allergy	1		
Injection site	6		
Alopecia	1		
Weight gain	6		
Weight loss	5		
Neurologic	8	1	
Psychiatric	1		
Neuro-clinical	16	4	
Metabolic	6		
Coagulation	4		
Other	29	2	