Phase 1 study of polyethylene glycol formulation of interferon α-2B (Schering 54031) in Philadelphia chromosome–positive chronic myelogenous leukemia

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Interferon α (IFN-α) therapy improves prognosis in Philadelphia chromosome (Ph)–positive chronic myelogenous leukemia (CML). Polyethylene glycol (PEG) attached to IFN-α prolongs its half-life and may offer better therapy. The aims of this phase 1 study were to define the maximal tolerated dose (MTD), dose-limiting toxicities (DLTs), and response with PEG IFN-α-2b. Twenty-seven adults with Ph⁺ CML in chronic or accelerated phases, in whom IFN-α treatment had failed, were studied. Patients had hematologic (9 patients) or cytogenetic resistance (12 patients) or intolerance to IFN-α (6 patients). PEG IFN-α-2b was given as a weekly subcutaneous injection starting at 0.75 μg/kg weekly and escalating to 1.5, 3, 4.5, 6, 7.5, and 9.0 μg/kg. The MTD was defined at 7.5 to 9 μg/kg; DLT included severe fatigue, neurotoxicity, liver function abnormalities, and myelosuppression. Longer administration of PEG IFN-α-2b resulted in chronic side effects not observed earlier, which defined the MTD and DLT. The proposed phase 2 dose of PEG IFN-α-2b was 6 μg/kg weekly. Among 19 patients with active disease, 7 (37%) achieved complete hematologic response (CHR); 2 (11%) had a cytogenetic response (complete). Among 8 patients treated in CHR, 7 (87%) improved cytogenetic response to complete (4 patients) or partial (3 patients). All 6 patients intolerant to IFN-α tolerated PEG IFN-α-2b; 4 improved their cytogenetic response. The results show that PEG IFN-α-2b is easier to deliver (once weekly), better tolerated, and perhaps more effective than IFN-α. (Blood. 2001;98:1708-1713)

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Introduction

Interferon α (IFN-α) therapy has been associated with improved prognosis in several cancers including chronic myelogenous leukemia (CML), lymphomas, multiple myeloma, renal cancer, and melanoma.[1-7] In Philadelphia chromosome (Ph)-positive (Ph⁺) CML, single-arm and randomized studies have demonstrated the benefit of IFN-α alone or in combination with cytosine arabinoside (ara-C) in improving outcome of patients with CML.[8-18]

Patient compliance to prolonged treatment with IFN-α in CML is an important factor for achieving clinical benefit.[1-3,19] Antitumor efficacy appears related to higher dose schedules of IFN-α daily therapy.[1,20,21] Similarly, trials in CML suggest that an increased area under the curve (AUC), and associated prolonged tumor exposure to IFN-α, may be important in mediating the antileukemic effects. Therapy with IFN-α is cumbersome and associated with significant side effects requiring dose reductions and temporary or permanent treatment interruptions in 10% to 50% of patients.[1-3]

Polyethylene glycol (PEG) is a linear, hydrophobic, uncharged, flexible polymer available in a variety of molecular weights.[22,23] A semisynthetic formulation (protein-polymer conjugate of IFN-α-2b) was developed by attaching a single PEG 12 000 molecule to the ε amino group of selected lysine residues in the IFN-α-2b molecule or the N-terminal amino acid.[24] PEG modification of proteins has led to the development of several PEG-proteins of current or future potential importance in therapy, including PEG-asparaginase,[25,26] PEG-erythropoietin,[27] PEG-granulocyte colony stimulating factor, recombinant PEG human megakaryocyte growth and development factor,[28,29] and others.[30,31] PEG modification of proteins prolongs their plasma half-life, reduces antigenicity and immunogenicity, and reduces sensitivity to proteolysis.[32,33] The new PEG-proteins may also at times be more effective than the unmodified molecules.[25,27,32-35]

We hypothesized that the new PEG IFN-α-2b, with its significantly prolonged plasma half-life from minutes to days, may allow easier treatment schedules (weekly instead of daily injections). By reducing immunogenicity and antigenicity, and by reducing access of the larger molecule to specific organs, it may also be associated with a lower incidence of side effects and improved patient tolerance and compliance. Finally, prolongation of plasma half-life and subsequent increase in AUC may enhance the therapeutic efficacy of PEG IFN-α-2b compared with IFN-α-2b. This report summarizes our phase 1 experience with PEG IFN-α-2b in patients with CML. In addition to defining the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD), we present detailed plasma pharmacokinetic studies and analyze tolerance and response to PEG IFN-α-2b following exposure to IFN-α therapy.

Patients and methods

Study group

Adults aged 18 years or older referred to or treated at our institution with a diagnosis of Ph⁺ CML were eligible. Entry criteria required (1) failure on

Table 1. Characteristics of the 27 study group patients

Characteristic	No.
Age at least 60 y [median]	3 [47]
Splenomegaly	2
Disease phase	
Chronic	17
Second chronic	1
Accelerated	9
Duration of disease (mo)	
Fewer than 12	2
12-36	7
More than 36	18
Hemoglobin (< 10 g/dL)	1
WBC ($> 20 \times 10^9$/L)	8
Platelets ($> 450 \times 10^9$/L)	6
Reason for change from IFN-α	
Hematologic resistance/partial hematologic response	4/5
Unsatisfactory cytogenetic response	12
Toxicities with IFN-α	6
Philadelphia chromosome percent status before PEG IFN-α-2b	
100%	20
35%-90%	4
15%-30%	3
Disease status at start of therapy	
Active	19
CHR	8

prior IFN-α therapy; (2) adequate performance status (ECOG performance 0-2), adequate liver (bilirubin, aspartate aminotransferase [AST], alanine aminotrasnferase [ALT] $\leq 2 \times$ normal) and renal functions (creatinine ≤ 2 mg/100 mL) and cardiac status; and (3) absence of serious neuropsychiatric complications, unless directly related to prior IFN-α therapy.

Failure on IFN-α could be because of (1) hematologic resistance defined by a failure to achieve a complete hematologic response (CHR) after 6 months of IFN-α therapy or rising white blood cell (WBC) count above 12×10^9/L despite optimal IFN-α–based therapy; (2) unsatisfactory cytogenetic response defined as lack of Ph suppression after 12 months or more of IFN-α therapy, Ph suppression to 35% Ph⁺ cells or more after 18 or more months of IFN-α therapy, or loss of cytogenetic response ($> 30\%$ increase in Ph⁺ metaphases); or (3) significant toxicity defined as grade 3 to 4 side effects.

Patients in blastic phase of CML were not eligible.[36] Patients in accelerated phase of CML, as previously defined,[37] were not eligible to be treated, except if they had clonal evolution as the only accelerated phase criterion. One patient was registered and later re-evaluated as having more than 15% blasts (patient 26 in Table 5). He was analyzed as part of the study group. All patients signed the appropriate informed consent, as required by institutional guidelines.

Therapy

Treatment with PEG IFN-α-2b was given as a single subcutaneous (SQ) injection weekly. Patients were taught self-injections and were observed as

outpatients for 1 month of treatment prior to continuing therapy under the care of their referring physicians. The starting dose schedule, based on 2 previous phase 1 studies in normal volunteers and in patients with compensated chronic hepatitis C, was 0.75 μg/kg SQ weekly.[38,39] Subsequent dose escalations were to 1.5, 3, 4.5, 6, 7.5, and 9 μg/kg weekly.

The phase 1 study followed the classical "3 + 3 design" used in most phase 1 studies. Three patients were entered at one dose level and observed for at least 3 weeks. If none of the 3 experienced grade 3 or worse toxicity, subsequent patients were entered on the next dose level. If 1 of 3 patients experienced grade 3 or worse toxicity, 3 more patients were treated at the same dose level. If 1 of 6 patients experienced grade 3 or worse toxicity, subsequent patients were entered at the next dose level. If 3 or more patients (of 3-6 depending on the details of the level) experienced grade 3 or worse toxicity, the DLT was exceeded and subsequent patients were treated at the next lower dose level, or a dose in between depending on the experience at the previous level. If 2 of 6 patients experienced grade 3 toxicity at a particular dose level, it defined the DLT and MTD, and the recommended dose for phase 2 studies was then defined at a dose level below the MTD.

Pretreatment and follow-up studies

Pretreatment evaluation required history and physical examination, complete blood counts, differential and platelet counts, serum chemistries (SMA12) including liver and renal functions, bone marrow aspiration for morphology and cytogenetic analysis, and additional studies as indicated. All patients had received prior IFN-α therapy. Documentation of prior IFN-α therapy response, dose schedule, and toxicities was performed when such information was available.

Follow-up studies included complete blood count, platelet and differential at least weekly for 4 weeks, then every 2 to 4 weeks; SMA12 weekly for 4 weeks, then every 4 to 8 weeks; marrow aspiration and cytogenetic analysis at 6 weeks, 3 months, and then every 3 to 6 months on therapy.

Pharmacokinetic studies of PEG IFN-α-2b

The pharmacokinetics of PEG IFN-α-2b were assessed using sparsely sampled serum concentration values obtained at 0, 24, 48, 72, and 168 hours after dosing at weeks 1 and 4. Serum PEG IFN-α-2b concentrations were determined using a validated electrochemiluminescence (ECL) assay with a lower limit of quantitation (LOQ) of 50 pg/mL. The assay was linear and reproducible between 50 and 2000 pg/mL.[40]

Individual serum PEG IFN-α-2b concentration-time data were used for pharmacokinetic analysis with model-independent methods.[41] Serum concentrations below the LOQ were reported as 0 pg/mL. The area under the serum concentration-time curve from time 0 to 168 hours (AUC[0-168 hours]) was calculated using the linear trapezoidal method. The average serum concentration (Cavg) was determined as follows: Cavg = [AUC(0-168 hr)] / 168 hr. The accumulation factor (R) was determined as follows: R = [AUC(0-168 hr), week 4] / [AUC(0-168 hr), week 1]. True C_{max}, T_{max}, and half-life values were not calculated due to the sparse sampling schedule.

Response and toxicity criteria

Response was defined as previously described.[1,2] A CHR required normalization of blood counts (WBC count $< 10 \times 10^9$/L, platelets $< 450 \times$

Table 2. Nonhematologic side effects with PEG IFN-α-2b

Dose level (μg/kg/wk)	No.	Fatigue, aches 2	Fatigue, aches 3-4	Depression 2	Neurotoxicity 2	Neurotoxicity 3-4	Fever, flu 2	Liver abnormalities 2	Liver abnormalities 3-4	Weight loss 1-2
0.75	3									
1.5	3	1								
3	3	1			1		1			1
4.5	3	1					1			
6	3	1		1			1		1	
7.5	6	3	1	1	1	1	1		1	1
9	6	2	2		1	2	1	1	1	1

Number of patients with toxicity grade is shown under each toxicity column.

Table 3. Hematologic side effects with PEG IFN-α-2b

Dose level (µg/kg/wk)	No.	Anemia		Thrombo-cytopenia		Granulo-cytopenia	
		2	3-4	2	3-4	2	3-4
0.75	3						
1.5	3				1		1
3	3					1	
4.5	3			1			
6	3					1	
7.5	6	1	1	1	2	1	1
9	6	1		3	2		2

Number of patients with toxicity grade is shown under each toxicity column.

10^9/L), no peripheral blasts, and disappearance of all signs and symptoms of CML, including palpable splenomegaly. CHR was further classified by the degree of cytogenetic response: complete if Ph$^+$ cells were 0%; partial if Ph$^+$ cells were 1% to 34%; minor if Ph$^+$ cells were 35% to 90%.

Toxicity grade was based on the National Cancer Institute (NCI) common toxicity criteria.[42]

Statistical considerations

Statistical methods were descriptive for response and side effects.

Results

Study group

Twenty-seven patients with Ph$^+$ CML were treated (Table 1). Their median age was 47 years (range, 21-66 years); 5 (18%) were women. The median duration of disease was 50 months (range, 7-144 months). Eighteen patients had chronic phase CML (1 was in second chronic phase); 9 patients had accelerated phase CML based on the following: blasts 15% or more, 1 patient; cytogenetic clonal evolution only, 8 patients.

Clonal evolution included double Ph, 2 patients; double Ph with trisomy 8, 1 patient; double Ph with trisomy 8 and isochromosome 17, 1 patient; trisomy 8, 1 patient; and other translocations [t(16;18), t(13;16), t(10;11)], 3 patients. The t(10;11) was also associated with additional changes.

Nineteen patients had active CML at the start of therapy; 8 patients were in CHR. Reasons for entering the study included hematologic resistance to IFN-α in 9 patients, unsatisfactory cytogenetic response (defined under "Patients and methods") in 12 patients, and intolerance to IFN-α in 6 patients. Patient 13 (Table 5) who had a cytogenetic response and clonal evolution [t(9;22) plus

t(16;18) in 15% of metaphases] is considered in the unsatisfactory cytogenetic response category. The median duration of IFN-α therapy in the 9 patients with hematologic resistance was 37 months (range, 8-118 months), and in the 12 patients with cytogenetic resistance 42 months (range, 12-92 months). Two patients in the group with intolerance to IFN-α still had a cytogenetic response at the start of PEG IFN-α-2b (patient 17, Ph 50%; patient 20, Ph 30%; Table 5), whereas the other 4 were 100% Ph$^+$. One patient who was not hematologically resistant to IFN-α (patient 9 in Table 5) had a different Ph$^+$ status between the last IFN-α evaluation and beginning PEG IFN-α-2b. In the evaluation for cytogenetic response, Ph status prior to beginning PEG IFN-α-2b was considered. The 6 patients intolerant to IFN-α (Table 5) were removed from the study for the following reasons: grade 3 toxicity with necrotizing skin reactions at the sites of injections (patient 1); grade 3 fatigue and difficult concentration, grade 2 joint aches, and shortness of breath (patient 9); grade 3 fatigue, aches, and depression, grade 2 nausea and stiffness (patient 14); grade 3 depression and grade 2 fatigue (patient 17); grade 3 pulmonary toxicity (patient 18); and grade 3 irritability and depression, and grade 2 fatigue and muscle and bone aches (patient 20).

Side effects

Toxicities at each dose level are detailed in Tables 2 and 3. At the dose level ranges of PEG IFN-α-2b 0.75 to 4.5 µg/kg SQ weekly, side effects were mild to moderate and included flulike symptoms (fever, chills) most prominent with the first injection, lasting for 24 to 48 hours and subsiding, fatigue, and aches. Tolerance to fever and flulike symptoms developed after multiple injections, although fatigue tended to increase. Only one patient experienced grade 2 nausea at 4.5 µg/kg, and another had grade 2 skin rash at 4.5 µg/kg (not shown for simplification). No other patients experienced such toxicities at these levels or at dose levels of 6 to 9 µg/kg.

At PEG IFN-α-2b 6 µg/kg, one patient each had grade 2 fatigue, grade 2 depression, fever, and flulike symptoms. One patient developed grade 3 liver toxicity (AST 353 IU/L, ALT 343 IU/L) after 9 weeks of therapy, which reverted to normal 4 weeks after treatment interruption and remained normal with reinstitution of one dose level reduction of PEG-IFN-α-2b (4.5 µg/kg SQ weekly). One patient developed neutropenia of 0.9×10^9/L after 16 months of therapy.

At 7.5 to 9 µg/kg, grade 3 fatigue and aches were observed in 3 of 12 patients, grade 3 neurotoxicity in 3 of 12 patients, and grade 3 liver abnormalities in 2 of 12 patients. Neurotoxicity included apathy, difficulty in thinking and concentration, and memory

Table 4. Response to PEG IFN-α-2b by disease status and prior response to IFN-α

	Treated	PHR	CHR	Cytogenetic response		
				Minor	Partial	Complete
Disease status						
Active	19	3	7	—	—	2
CHR	8	NA	NA	—	3	4
Status prior to therapy						
Hematologic resistance to IFN-α	9	—	4	—	—	—
Cytogenetic status prior to PEG IFN-α-2b						
Ph 95%-100%	11	—	NA	—	—	2
Ph 50%-75%	4	—	NA	—	2	2
Ph 15%-35%	3	—	NA	—	1	2
Intolerance to IFN-α	6	—	—	—	1	3

Entries are numbers of patients. Patient with accelerated phase CML and ≥ 15% blasts returned to second chronic phase, but is evaluated as resistant because he did not achieve PHR or CHR (patient 26 in Table 5).

NA indicates not applicable.

Table 5. Details of patient and disease characteristics and response to PEG IFN-α-2b

| Patient no. | Age (y) | CML duration (mo) | PEG IFN-α-2b dose (µg/kg/wk) | Last IFN-α response | CML phase (active/CHR) | WBC pretreatment (× 10⁹/L) | Percent Ph⁺ cells | | Overall response on PEG IFN-α-2b |
							Pre-PEG IFNα-2b	Lowest on therapy	
1*	57	52	0.75	CHR	Second CP-A	15.6	100	NA	Resistant
2	23	97	0.75	PHR	Acc-A	25.4	100	NA	Resistant
3	60	43	0.75	PHR	CP-A	14.6	100	NA	Resistant
4	55	58	1.5	CHR	CP-A	13.3	100	100	CHR
5	21	12	1.5	PHR	Acc-A	21.8	100	NA	Resistant
6	55	137	1.5	Resistant	CP-A	38.6	100	100	CHR
7	46	36	3	CHR	CP-A	48.2	100	NA	Resistant
8	66	21	3	Resistant	CP-A	73.6	100	100	CHR
9*	59	22	3	Minor CG	CP-A	18.2	100	0	Complete CG
10	40	38	4.5	CHR	CP-A	12.3	95	NA	Resistant
11	31	79	4.5	Resistant	CP-A	14.7	100	100	CHR
12	35	109	4.5	CHR	Acc-CHR	6.4	100	NA	Resistant
13	59	8	6	Partial CG	Acc-CHR	4.4	15	0	Complete CG
14*	56	7	6	CHR	CP-A	11.9	100	0	Complete CG
15	34	99	6	Minor CG	CP-CHR	8.0	50	0	Complete CG
16	61	138	7.5	Resistant	Acc-A	53.2	100	100	Resistant
17*	41	60	7.5	Minor CG	CP-CHR	7.9	50	0	Complete CG
18*	33	78	7.5	CHR	CP-A	9.3	100	NA	Resistant
19	47	50	7.5	CHR	Acc-A	19.0	100	100	PHR
20*	50	25	7.5	Partial CG	CP-CHR	4.6	30	5	Partial CG
21	50	144	7.5	PHR	CP-A	52.0	100	100	CHR
22	45	45	9	CHR	Acc-A	13.6	100	100	PHR
23	33	90	9	Partial CG	CP-CHR	6.5	20	0	Complete CG
24	41	106	9	CHR	CP-A	10.5	100	100	PHR
25	47	30	9	Minor CG	Acc-CHR	5.4	69	17	Partial CG
26†	56	50	9	PHR	Acc-A†	71.1	100	100	Second CP
27	54	14	9	Minor CG	CP-CHR	7.2	75	25	Partial CG

CP indicates chronic phase; Acc, accelerated phase; NA, not applicable; A, active disease; CG, cytogenetic; Minor CG, Ph 35%-90%; partial CG, Ph 1%-34%; complete CG, Ph 0%.

*Entered for IFN-α intolerance.

†Accelerated blasts ≥ 15%.

problems. Thrombocytopenia less than 50×10^9/L was observed in 2 of 6 patients at 7.5 µg/kg, and in 2 of 6 patients at 9 µg/kg. Granulocytopenia less than 0.5×10^9/L was observed in 1 of 6 patients at 7.5 µg/kg and in 1 of 6 patients at 9 µg/kg. Although the toxicity evaluation to escalate to the next dose level was after 1 month of therapy, some of the grade 3 toxicities developed after longer periods of therapy. This explains the grade 3 to 4 myelosuppression at 1.5 µg/kg not accounted for in the dose escalation because it occurred later. Other grade 3 to 4 hepatic and neurotoxicities also occurred at times beyond the first month of study. Thus, the cumulative experience with longer therapy indicated that PEG IFN-α-2b dose schedules of 7.5 to 9 µg/kg weekly defined the MTD with reasonable certainty among the 12 patients treated at these 2 dose levels. The DLTs were defined by severe fatigue,

severe neurotoxicity, liver dysfunction, and severe myelosuppression as defined by the NCI criteria. None of the marrow toxicities were associated with complications such as febrile infections or need for transfusions. The PEG IFN-α-2b dose schedule of 6 µg/kg weekly was the recommended dose as a single agent for phase 2 studies, one dose below the MTD, considering the small numbers of patients treated.

Response and tolerance

Response by disease status at start of PEG IFN-α-2b (active, CHR), and by prior last IFN-α response are shown in Table 4. Among 19 patients with active disease at the start of therapy, 7 achieved CHR (37%), and 3 had a partial hematologic response (PHR), for an overall response rate of 53%. Two patients achieved a complete

Table 6. Follow-up cytogenetic studies among patients with improved cytogenetic response on PEG IFN-α-2b

| Patient | Percent Ph⁺ metaphases on PEG IFN-α-2b therapy | | | | | | |
	Pretreatment	Best (overall)	At 3 months	At 6 months	At 9 months	At 12 months	After 12 months [month of therapy]
9	100	0	—	95	95	100	65 [18], 40 [26], 0 [30]
13	15	0	10	10	0	15	0 [14], 30 [17], 10 [20], 65 [24], 25 [26]
14	100	0	100	95	95	75	55 [15], 0 [25]
15	50	0	60	40	30	13	0 [16], 25 [25]
17	50	0	0	0	0	0	0 [16], 0 [24]
20	30	5	14	5	35	Insufficient	10 [13], 30 [17], 45 [24]
23	20	0	15	0	0	0	5 [19]
25	69	17 (1 mo)	90	90	100	—	—
27	75	25	75	47	25	—	25 [21]

cytogenetic response (patients 9 and 14 in Table 5). One patient in accelerated phase with 15% or more blasts returned to a second chronic phase (patient 26 in Table 5). Among 8 patients entered into the study in CHR, 7 achieved or improved their cytogenetic response. Four patients with minor cytogenetic responses at the start of PEG IFN-α-2b therapy improved to partial cytogenetic response (2 patients: Ph from 75% to 25%, and Ph from 69% to 17%, respectively), and to complete cytogenetic response (2 patients; both from Ph 50% to 0%). The other 3 patients starting with a partial cytogenetic response either improved their response (1 patient: Ph 30% to 5%), or achieved a complete cytogenetic response (2 patients: Ph from 20% to 0% and from 5% to 0%, respectively). All 6 patients treated for IFN-α intolerance were able to tolerate PEG IFN-α-2b; 4 achieved a cytogenetic response, 1 partial and 3 complete.

Table 5 lists the individual patient and disease characteristics including prior response to IFN-α, disease status at the start of PEG IFN-α-2b, and response evaluation.
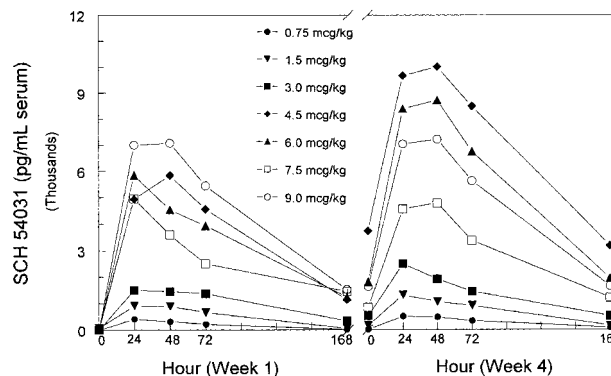
Table 6 details the follow-up cytogenetic studies among patients who achieved improved cytogenetic response with PEG IFN-α-2b. The median follow-up of patients is 25 months (range, 2-34 months). Currently, 24 of the 27 patients are alive, and 10 continue on PEG IFN-α-2b.

Pharmacokinetic studies

PEG IFN-α-2b was well absorbed following SQ administration to patients with CML (Table 7). Serum concentrations increased in a dose-related manner at week 1, but not at week 4, which may be due to the high interpatient variability and the small number of patients (Figure 1). There appeared to be no dose-related changes in the accumulation of PEG IFN-α-2b (Table 7).

Figure 1. Concentration-time profiles. The mean concentration-time profiles of PEG IFN-α-2b are shown for different dose levels (0.75-9.0 μg/kg) as measured on week 1 (dose 1) and week 4 (dose 4).

half-lives were similar at 4.6 versus 2.3 hours; however, the elimination half-life was 8- to 10-fold greater for PEG IFN-α-2b compared with IFN-α-2b (44 versus 4-5 hours). Mean apparent clearance was 10-fold less for PEG IFN-α-2b and the volume of distributions similar for both compounds.

In our phase 1 study of PEG IFN-α-2b in CML, the findings were encouraging. The DLT was defined by significant thrombocytopenia, but side effects including fatigue, weight loss, and neurotoxicity were observed. The MTD was defined at PEG IFN-α-2b dose of 7.5 to 9 μg/kg SQ weekly. The proposed dose of PEG IFN-α-2b for phase 2 studies is 6 μg/kg weekly. However, as with many other phase 1 to 2 studies this dose has to be evaluated according to the cumulative experience with longer durations of therapy, toxicities with combinations (eg, with ara-C), and with different characteristics of study group (eg, no prior IFN-α exposure, older patients).

The predicted AUC comparative dose to PEG IFN-α-2b 0.3 μg/kg weekly is IFN-α 9 MU weekly. Thus the PEG IFN-α-2b dose of 6 μ/kg weekly chosen for phase 2 studies is equivalent to IFN-α-2b 180 MU weekly, that is, 27 MU daily (about 15 MU/m^2 daily). This dose is at least 3 times the IFN-α doses used in previous CML studies, without increased toxicities. This may explain the superior anti-CML efficacy of PEG IFN-α-2b compared with IFN-α.

Of interest were the favorable results observed in particular study groups. For example, among 9 patients with definite hematologic resistance to prior optimal IFN-α therapy, 4 patients (44%) demonstrated response to PEG IFN-α-2b. Among patients starting with 100% Ph$^+$ disease, 2 of 11 had improved cytogenetic response (Table 4). Cytogenetic responses improved in 9 of 27 patients treated (33%). Finally, all 6 patients treated because of intolerance

Discussion

Two previous phase 1 studies of PEG IFN-α-2b had been conducted that defined our current starting dose.[38,39] In normal volunteers randomized to receive a single SQ injection of PEG IFN-α-2b (up to 0.5 μg/kg) or IFN-α-2b, side effects included flulike symptoms, redness at the injection site, headache, fatigue and malaise, and myelosuppression. Among patients with chronic active hepatitis C, PEG IFN-α-2b doses up to 1.5 μg/kg weekly were well tolerated without DLT, and a similar spectrum of side effects observed. Side effects were less severe at PEG IFN-α-2b doses up to 1 μg/kg relative to IFN-α-2b 3 MU (million units) 3 times weekly. Pharmacokinetics studies showed better profiles for PEG IFN-α-2b compared with IFN-α-2b. The mean absorption

Table 7. Mean pharmacokinetic parameters

Parameter	PEG IFN-α-2b weekly dose (μg/kg)						
	0.75	1.5	3.0	4.5	6.0	7.5	9.0
Week 1							
n	3	3	3	3	3	6	6
Cavg (pg/mL)	184	513	1 013	2 907	3 243	3 062	4 393
AUC(0-168 h) (pg/h/mL)	30 984	86 244	170 196	488 440	544 752	514 416	738 072
Week 4							
Cavg (pg/mL)	288	725	1 338	6 931	5 548	3 006	4 592
AUC(0-168 h) (pg/h/mL)	48 384	121 868	224 756	1 164 476	932 124	505 022	771 410
R	1.54	1.59	1.36	2.99*	1.65	1.26	1.19

*Including subject 11 (R = 1.49, excluding subject 11).

to IFN-α were able to tolerate PEG IFN-α-2b, and 4 of them had a favorable response (Table 4). This indicates the better general tolerance of patients to PEG IFN-α-2b compared with IFN-α. Thus, of a total of 27 patients in whom IFN-α therapy had failed, 13 (48%) had a favorable response to PEG IFN-α-2b (either CHR or improved cytogenetic response).

PEG IFN-α-2b was well absorbed following SQ administration in CML. PEG IFN-α-2b serum concentrations increased in a dose-related manner at week 1 but not at week 4 (Table 7). This may have been due to high interpatient variability and the small number of patients assessed in this study.

In summary, PEG IFN-α-2b appears to provide easier schedule delivery, better tolerance, and perhaps improved efficacy compared with regular IFN-α. Future studies will evaluate PEG IFN-α-2b in combinations with other active anti-CML agents such as cytarabine, homoharringtonine, and the BCR-ABL tyrosine kinase inhibitor STI571 (Gleevec, Novartis, East Hanover, New Jersey), as well as in front-line CML therapy.

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