Chronic Myeloid Leukemia

Polyethylene glycol interferon-α2b alone or in combination with low-dose Ara-C in patients newly diagnosed with chronic myeloid leukemia

Thirty-five patients newly diagnosed with chronic myeloid leukemia received pegylated interferon α-2b (PEG-IFN) alone or combined with intermittent Ara-C for a median of 6.5 months (range: 1.4-19.2). The median weekly PEG-IFN dose was 4.0 μg/kg. Complete hematologic, major and complete cytogenetic responses were observed in 73%, 32% and 14%, respectively. Extra-hematologic side-effects were frequent and 20% of patients had grade III-IV hematologic toxicity.

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A semisynthetic formulation of interferon (IFN) has been developed by attaching a single polyethylene glycol (PEG) molecule to prolong the drug's plasma half-life and reduce its toxicity.[1] Imatinib achieves complete cytogenetic responses (CCR) in most patients newly diagnosed with CML,[2] but complete molecular responses are rare.[3] Consequently, strategies involving imatinib in combination with other drugs, for example PEG-IFN, are currently being explored.[4,5]

From November 2001 to November 2002, 35 individuals aged 18-70 years, with Ph+ CML (<9 months from diagnosis), normal renal, hepatic and cardiac function, and an ECOG PS <2, were enrolled into a phase II study. Pregnancy and HIV-positivity were exclusion criteria. After cytoreduction with hydroxyurea, patients were scheduled to receive weekly subcutaneous injections of PEG-IFN α-2b (Schering-Plough, Spain) at 6.0 μg/kg;[1] hydroxyurea was stopped when the PEG-IFN was started. Given the poor tolerance of the first 4 patients to the above dose, the remaining 31 were given a lower starting dose of 2.0 μg/kg, with 1.0 μg/kg increases being applied every two weeks up to a maximum of 6.0 μg/kg. Once a tolerable dose of PEG-IFN had been identified in each patient, monthly 10-day cycles of subcutaneous Ara-C (20 mg/m^2, maximum 40 mg) were added. During the first two months, patients were controlled on a fortnightly basis, and then every four weeks once the 6.0 μg/kg or the maximum tolerated dose had been reached. Cytogenetic analysis was performed every 6 months or at treatment withdrawal. Patients went off study if major cytogenetic response (MCR) was not achieved by one year after treatment initiation in the case of unacceptable toxicity or by request. The WHO criteria were used to assess toxicity.

Table 1 summarizes the patients' main characteristics at diagnosis. The median time between diagnosis and treatment was 3.2 months (range: 0.1-8) and the median duration of PEG-IFN treatment was 6.5 months (range: 1.4-19.2). Three patients discontinued therapy within 3 months (intolerance, n=2; transplantation, n=1). One patient had severe side-effects after the first PEG-IFN dose (6.0 μg/kg) and following reintroduction at 2.0 mg/kg he developed severe respiratory failure leading to death. Ten patients went off study at 3-6

Table 1. Main characteristics at diagnosis of 35 patients newly diagnosed with chronic phase CML treated with PEG-IFN alone or combined with low-dose Ara-C.

Characteristics	*No. of patients (%)*
Median age, range	55 years, 23-69
Gender (M/F)	23/12
Palpable splenomegaly	13 (37)
Hb ≤ 100 g/L	2 (6)
WBC count ≥ 50×10^9/L	18 (51)
Platelet count ≥ 400×10^9/L	17 (49)
Blood blasts ≥ 1%	12 (35)
Sokal risk groups *	
Low	16 (49)
Intermediate	13 (39)
High	4 (12)
Hasford risk groups **	
Low	13 (43)
Intermediate	14 (47)
High	3 (10)

** n= 33; ** n=30*

Table 2. Main side effects of PEG-IFN + low-dose Ara-C treatment in 35 patients newly diagnosed with chronic phase CML.

Side effect	*N. of patients (%)*			
	PEG-IFN alone (n=19)		*PEG-IFN + Ara-C (n=16)*	
	Any grade	*Grade III-IV*	*Any grade*	*Grade III-IV*
Fever	18 (95)	3 (16)	12 (75)	2 (12)
Performance status decrease*	16 (84)	10 (53)	12 (75)	5 (31)
Weight loss	10 (53)	1 (5)	7 (44)	0
Fatigue	13 (68)	2 (10)	11 (69)	1 (6)
Anorexia	8 (42)	0	6 (38)	0
Muscle/bone pain	13 (68)	1 (5)	12 (75)	2 (12)
Nausea/vomiting	5 (26)	0	4 (25)	0
Diarrhea/abdominal pain	5 (26)	0	6 (38)	0
Neurologic changes/depression	9 (47)	0	5 (31)	1 (6)
Respiratory distress	1 (5)	1 (5)	0	0
Headache	3 (16)	0	3 (19)	0
Mucositis	1 (5)	0	2 (13)	0
Local reaction	3 (16)	0	4 (25)	0
Liver function abnormalities	8 (47)	1 (5)	7 (44)	2 (12)
Hematologic toxicity				
Neutropenia	10 (53)	6 (32)	5 (31)	1 (6)
Thrombocytopenia	11 (58)	3 (16)	8 (50)	0
Anemia	5 (26)	0	6 (38)	0

** WHO grade.*

months of treatment due to intolerance. Among the 31 patients who received PEG-IFN for >3 months, the median dose per cycle was 4.0 μg/kg (range: 1.5-5.9) and the median maximum dose was 5.0 μg/kg (range: 1.7-6.0), with only 15 patients reaching the 6.0 μg/kg dose. Nineteen patients did not receive Ara-C (early withdrawal, n=4; PEG-IFN hematologic toxicity, n=15). In the remainder, the median number of Ara-C cycles was 2 (range: 1-10).

Of the 22 patients not in complete hematologic response (CHR) at the start of treatment, 16 (73%) achieved a CHR by a median of 3 weeks (range: 2-12). In the 22 evaluable patients, the best observed response was a MCR in 32%, including 14% who had a CCR. Extra-hematologic toxicity is shown in Table 2. One patient developed fever, chills and muscle and bone pain at the time of the first PEG-IFN dose (6.0 μg/kg). This patient was managed with hydroxyurea for three months, and then PEG-IFN (2.0 μg/kg) was reintroduced. Immediately after, he developed fever, acute respiratory distress and lung infiltrates. Microbiological studies were negative and, despite standard measures, the patient died. Grade II-IV neutropenia was recorded in 20% of cases but only one patient required hospital admission because of infection.

With a median follow-up of 17.2 months (range: 3.7-24.8), two patients died (PEG-IFN toxicity and transplant complications, one case each), one remains on PEG-IFN and maintains a CCR at 19 months, two switched to regular IFN and attained CCR, four received a transplantation and one switched to hydroxyurea. The remaining 26 were converted to imatinib; 19 of 22 assessed for response achieved a CCR. Talpaz *et al.* reported the results of PEG-IFN treatment in 27 patients with chronic or accelerated phase CML resistant/intolerant to IFN.[1] The starting dose was 0.75 μg/kg/week and the recommended weekly dose 6.0 μg/kg, since higher doses involved substantial hematologic and extra-hematologic toxicity. Treatment was effective, especially in patients already in CHR. Garcia-Manero *et al.*[6] administered PEG-IFN plus Ara-C to 76 patients with early chronic phase CML. The starting dose was initially 6.0 μg/kg but, due to toxicity, the starting dose was then reduced to 4.5 μg/kg. CHR was obtained in 73% of cases and MCR in 56%, including 21% CCR. It was recommeded that the PEG-IFN dose be decreased to 3.0 μg/kg or less. Michallet *et al.*,[7] in a randomized study of 344 newly-diagnosed patients, compared PEG-IFN α-2b and standard IFN, reporting 23% and 21% MCR, respectively, at one year, with similar toxicity. The results of our study are comparable, although we found more toxicity. The preliminary results of two studies of imatinib plus PEG-IFN in newly-diagnosed CML indicate the efficacy of this combination but also its substantial toxicity.[4,5]

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Chronic Myeloproliferative Disorders

FIP1L1-PDGFRA and *c-kit* D816V mutation-based clonality studies in systemic mast cell disease associated with eosinophilia

Laboratory methods to detect both *FIP1L1-PDGFRA* and *c-kit* D816V mutations were combined with immunomagnetic cell separation to study the extent of clonal involvement by both myeloid and lymphoid cells in 3 patients with systemic mastocytosis associated with eosinophilia. The results suggested an early stem cell origin for the *FIP1L1-PDGFRA* mutation.

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Certain mutations in either the stem cell (*c-kit*) or platelet-derived growth factor receptor (*PDGFRA*) genes have been pathogenetically linked to systemic mast cell disease (SMCD) (e.g. *c-kit* D816V, *FIP1L1-PDGFRA*).[1,2] While *FIP1L1-PDGFRA*+ SMCD is invariably associated with prominent blood eosinophilia,[2] the D816V *c-kit* mutation has been demonstrated in both the presence[2] and absence[3] of associated eosinophilia. The availability of highly reliable laboratory assays to detect these specific mutations has offered the opportunity for lineage-specific clonal studies in SMCD. Accordingly, *c-kit* D816V mutation-based clonality studies have previously demonstrated clonal involvement of both myeloid (monocytes, neutrophils, eosinophils, erythrocytes) and lymphoid cells (B or T lymphocytes) in both indolent and aggressive SMCD.[4-8] In the current study, we used immunomagnetic bead cell separation techniques in combination with either fluorescence *in situ* hybridization (FISH) or polymerase chain reaction (PCR)-based DNA sequencing to study the extent of clonal involvement in various cell types of myeloid as well as lymphoid lineage in both *FIP1L1-PDGFRA*+ and *c-kit*