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Feasibility of Pegylated Interferon in Children and Young Adults with Resected High-Risk Melanoma

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Abstract

Background—Pegylated interferon α -2b (IFN α -2b) improves disease-free survival in adults with resected stage III melanoma. We conducted a study to determine the feasibility and safety of incorporating pegylated IFN α -2b as adjuvant therapy in the treatment of children and adolescents with high-risk melanoma. Pharmacokinetic studies of IFN α -2b and neuropsychological and quality of life (QOL) assessments were performed.

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CONFLICT OF INTEREST STATEMENT

Alberto Pappo is a consultant for Ziopharm Oncology, Inc. All other authors report no conflict of interest.

Patient and Methods—Eligible patients with resected AJCC Stage IIC, IIIA and IIIB cutaneous melanoma received non-pegylated IFN α -2b 20 million units/m²/day intravenously 5 days per week for 4 weeks (induction) followed by pegylated IFN α -2b 1 mcg/kg/dose weekly subcutaneously (SQ) for 48 weeks (maintenance).

Results—Twenty-three patients (15 females, median age 10 years) were enrolled. All patients completed induction therapy; whereas, 5 patients did not complete maintenance therapy either because of recurrent disease (n=2) or toxicity (n=3). The most common grade 3-4 toxicities of pegylated IFN α -2b were neutropenia (35%) and elevated liver transaminases (17%). The median non-pegylated IFN α -2b AUC_{0-∞} (5,026 pcg*hr/mL) was similar to adults. The median pegylated IFN α -2b exposure (48,480 pcg*hr/mL) was greater than the cumulative weekly exposure for non-pegylated IFN α -2b administered SQ three times per week (TIW). Validated measures demonstrated an improvement in QOL scores and no decline in psychological functioning over the course of therapy.

Conclusions—Pegylated IFN α -2b 1 mcg/kg/dose SQ weekly as maintenance therapy in children and adolescents with high-risk melanoma is feasible with tolerable toxicity and appears to yield higher exposures than non-pegylated IFN α -2b administered SQ TIW.

Keywords

pegylated interferon; melanoma; childhood; pharmacokinetics; high-risk; adjuvant therapy

INTRODUCTION

Compared to adults, the incidence of cutaneous melanoma in the pediatric population is low, with only ~400 new cases diagnosed in the United States per year in patients <20 years of age.[1] Due to the rarity of the disease in this patient population, the treatment generally follows the guidelines outlined for adult patients with melanoma and prospective clinical trials are rare but an area of need as the incidence in the adolescent population is increasing by about 3% per year.[1]

Interferon α -2b (IFN α -2b) has been used as adjuvant therapy in adult patients with surgically resected cutaneous melanoma who are at high risk of recurrence.[2] Various dosages and schedules of IFN α -2b have been evaluated in clinical trials with variable benefit.[3] The studies using high dose IFN α -2b consistently demonstrate an advantage in prolonging time to progression as well as a favorable cost-effectiveness ratio.[4-8] A commonly used IFN α -2b regimen is 20 million units/m²/day intravenously, five times per week for 4 weeks (induction) followed by 10 million units/m²/dose subcutaneously, three times per week (TIW) for 48 weeks (maintenance). The feasibility of administration of this regimen has been reported in a small number of pediatric patients with melanoma and has proven to be tolerable in children.[9-11]

A formulation of IFN α -2b, peginterferon α -2b (PEG Intron®; Merck, Inc), has been developed that contains a single straight-chain molecule of polyethylene glycol (PEG) covalently linked to histadine-34 on IFN α -2b. The PEG moiety decreases clearance, thus increasing the plasma half-life of the IFN α -2b from approximately 4 hours to 40 hours. As

a result, the drug can be administered once weekly.[12] Preclinical and clinical studies indicate that the biological activity of IFN α -2b is similar, if not better than conventional interferon.[13, 14] Recently, pegylated IFN α -2b was approved for use in adult patients with high-risk melanoma based on the results of the EORTC 18991 trial in which significant improvement in disease-free survival (DFS) was observed in patients with resected stage III melanoma.[15] The adverse events in adults appear to be similar to non-pegylated IFN α -2b.[16, 17]

Based on the potential benefit observed with pegylated IFN α -2b in adult patients with melanoma and the more convenient once weekly dosing, we conducted a study to determine the feasibility and safety of pegylated IFN α -2b once weekly as a subcutaneous injection following an initial induction phase of high dose IFN α -2b in children and adolescents with resected 2002 American Joint Committee on Cancer (AJCC)[18] Stage IIC, IIIA or IIIB cutaneous melanoma.

PATIENTS AND METHODS

Patients

Eligibility criteria included: age \geq 21 years, resected AJCC Stage IIC, IIIA or IIIB cutaneous melanoma, Karnofsky/Lansky performance score \geq 50 and no prior therapy for melanoma except surgery. Other organ-specific and prior therapy inclusion/exclusion criteria are provided in Supplementary Materials.

Written informed consent was obtained from patients, parents, or legal guardians, with assent as appropriate. The protocol was approved by the institutional review board of each of the three institutions participating in the study: St. Jude Children's Research Hospital, Rady Children's Hospital and MD Anderson Cancer Center.

Treatment Plan

All patients underwent a primary wide local excision (WLE) with a minimum of 1–2 cm margin (if anatomically feasible) surrounding the primary lesion or biopsy scar and a sentinel lymph node biopsy (SLNB). If the sentinel lymph node(s) was positive for disease, then a complete lymph node dissection (CLND) of the involved lymph node basin was performed. Following surgery, patients received induction therapy with recombinant IFN α -2b (*Intron A*®, Merck, Inc.) 20 million units/m² per day intravenously on 5 consecutive days per week for 4 weeks. Patients were premedicated with acetaminophen and/or ibuprofen. Following induction therapy, patients received pegylated IFN α -2b 1 mcg/kg/dose weekly subcutaneously for 48 weeks. This dosage of pegylated IFN α -2b was selected based on the results of pharmacokinetic studies in patients with chronic hepatitis C demonstrating a roughly equivalent area under the curve (AUC) to 10 million units TIW of IFN α -2b (dose used in maintenance phase of adult regimen).[14] IFN α -2b and pegylated IFN α -2b were supplied by Schering-Plough/Merck, Inc.

Evaluations, Toxicity Grading and Dose Modifications

Evaluations at baseline, during and after completion of therapy are outlined in Supplementary Materials. Toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Dose modification was required for any grade 3 or 4 non-hematologic toxicity, with exception of the following toxicities: any drug-related grade fever, chills, pain or fatigue, medically managed grade 3 or 4 nausea or vomiting, grade 3 infection or grade 3 electrolyte abnormalities responsive to oral supplementation. In addition, dose modification was required for any grade 2 cardiopulmonary toxicity, grade 2 elevation in BUN/creatinine, grade 4 neutropenia, or grade 4 thrombocytopenia. Dose modification required holding IFN α -2b or pegylated IFN α -2b therapy until symptoms resolved to \leq grade 1. A 25% reduction in dosage occurred after the first interruption, 50% reduction after the second interruption and discontinuation if a third dosage modification was required. If $>$ grade 1 toxicity persisted for >2 weeks from when the next dosage of drug was due, therapy was discontinued. IFN α -2b or pegylated IFN α -2b therapy was discontinued for any grade 4 cardiopulmonary toxicity, grade 4 mood alteration or grade 3 elevations in BUN/creatinine.

Missed doses of IFN α -2b were not made up. Dose re-escalation was not permitted. Patients who did not meet the protocol specified off therapy criteria for toxicity could remain on therapy in the absence of recurrent disease.

Quality of Life and Psychologic Assessments

In consenting patients, parent proxy and patient reported QOL outcomes were assessed using the Pediatric Quality of Life Inventory (PedsQL v4.0) and the Pediatric Cancer Quality of Life Inventory (PedsQL v3.0).[19, 20] The Behavioral Assessment System for Children, 2nd Edition (BASC-2)[21] and the Behavioral Rating Inventory of Executive Function (BRIEF)[22] were administered to parents, assessing for any effects on behavior or mood in children undergoing study therapy. The QOL and psychological assessments were obtained at the time points shown in Table III.

Pharmacokinetics

In consenting patients, serial serum samples (3 mL) for pharmacokinetic studies of IFN α -2b were collected before the first dose week 1, day 1 of induction therapy and 1, 2, 4, 6, 8, 12 and 24 hours post infusion. Serial serum samples (3 mL) for pharmacokinetic studies of pegylated IFN α -2b were collected during maintenance therapy before the first dose and 24, 96 and 168 hours after the dose during weeks 5 and 28. In addition, pre-dose serum samples for pegylated IFN α -2b were collected on weeks 8, 12, 16, 44, and 52. Samples were analyzed for IFN α -2b or pegylated IFN α -2b concentrations by using the VeriKine Human Interferon Alpha ELISA Kit (PBL Assay Science) following the manufacturer's instructions and concentration-time data were analyzed by nonlinear-mixed effects modeling as implemented in NONMEM 7.3.[23] Details are provided in Supplementary Materials.

Statistical Methods

Event-free survival (EFS) and overall survival (OS) were estimated by the method of Kaplan-Meier.[24] The duration of OS was defined as the interval between time from study enrollment and death from any cause or last follow-up. The duration of EFS was defined as the interval between time from study enrollment and recurrence of disease, development of secondary malignancy, death or last follow-up. Patients who had not met criteria for an event were censored at the time of last follow-up.

Mixed-effects linear models for repeated measures were used to examine the mean change in total QOL, total cancer specific QOL, behavioral, and executive functioning scores over the course of the study. The unstructured correlation structure was selected to account for the correlation among repeated measurements made on the same patient for all models. A two-sided significance level of 0.05 was used for all statistical tests.

RESULTS

Patients

Twenty-three patients with resected AJCC Stage IIC, IIIA or IIIB melanoma were enrolled on study from June 2007 through September 2012. Patient characteristics are summarized in Table I.

Toxicity

Grade 3 or 4 and grade 1 or 2 toxicities related to induction and maintenance therapy are summarized in Table II and Supplemental Table SI, respectively.

All patients completed induction with IFN a-2b. The most common grade 3 or 4 toxicities were neutropenia (83%) and elevated liver transaminases (17%). Four patients required dose reductions, three for grade 3 elevation in liver transaminases and one for grade 4 neutropenia. Two patients had a delay in starting maintenance therapy. One had grade 3 hypertriglyceridemia and one had grade 4 neutropenia.

During maintenance, 5 (22%) patients did not complete pegylated IFN a-2b therapy; 3 were removed from protocol therapy because of unacceptable toxicity, including one each with grade 3 joint effusion, grade 3 elevation in aspartate aminotransferase and alanine aminotransferase, and grade 4 mood alteration (aggressive behavior). Two patients discontinued therapy due to recurrent disease. As with non-pegylated INF a-2b, the most common grade 3 or 4 toxicities were neutropenia (35%) and elevated liver transaminases (17%). Four patients required dose reductions, all due to grade 3 elevation in liver transaminases. Additionally, 4 patients required holding a weekly dose of pegylated interferon, one each for cholecystectomy, viral illness, hematochezia, and behavior issues deemed unrelated to therapy. Two patients did not receive the last dose of pegylated IFN a-2b for non-toxicity related reasons.

Thyroid abnormalities were present in 9 out of 23 participating subjects (39.1%). Autoimmune thyroiditis (i.e., thyroid peroxidase (TPO) and/or thyroglobulin (TGB) antibody titers > ULN) was diagnosed in 8 patients (present at baseline in 1). Only 2 patients

experienced resolution (negative antibody titers) during the study time. Among the 8 patients with autoimmune thyroiditis, 6 had abnormal thyroid function: 4 required replacement with levothyroxine, 1 remained asymptomatic and did not require replacement and 1 had a known prior diagnosis of Graves' disease, developed TPO and TGB antibodies but remained asymptomatic during the study period. One patient developed hypothyroidism during maintenance but had negative TPO and TGB autoantibody titers.

Non-thyroid related autoantibodies [anti-nuclear (ANA), anti-DNA, or anticardiolipin (ACA) antibodies] were detected in 12 patients (present at baseline in 5). One patient who had a low level ACA IgM prior to receiving interferon also developed a positive ANA and anti-DNA during therapy that resolved following the completion of therapy. In the remaining 7 patients, 5 developed positive ANA titers and 2 ACA IgM. All patients were asymptomatic except the one patient who developed a positive ACA IgM and had grade 3 joint pain and effusion. Five of the 12 patients with non-thyroid related autoantibodies also had thyroid related autoantibodies. Excluding patients with autoantibodies prior to interferon therapy, 10 patients developed autoantibodies (thyroid and/or non-thyroid related) while receiving interferon therapy. Of these patients, 3 of 7 with follow-up titers had no detectable autoantibody off treatment.

Outcome

The median follow-up from the time of enrollment was 37.8 months (range, 15.3–64.8 months). Twenty-one patients were alive without evidence of disease recurrence. One 18 year old patient with nodular melanoma of the upper back (ulcerated, Breslow thickness 6.2 mm, mitosis 7/mm²) who had a sentinel node (right axilla) negative for tumor at diagnosis, presented while on maintenance therapy with one isolated cervical lymph node detected by PET/CT. An excisional biopsy of the lymph node revealed malignant melanoma. This patient underwent a CLND followed by radiation to the involved nodal basin and is alive without disease 27 months after the regional recurrence. One patient has died. He was a 14 year old with a superficial spreading melanoma of the shoulder (ulcerated, Breslow Thickness >1.3 mm, mitosis 5/mm²) and a positive sentinel lymph node for tumor at diagnosis with no additional involved nodes found at the time of complete lymph node dissection. He presented with metastatic lung disease while on maintenance therapy and died of disease 18 months from diagnosis. Three-year estimates of OS and EFS are 95.2%±5.8% and 91.3%±7.5%, respectively.

Quality of Life and Psychological Functioning

Mean total scores for QOL and psychological assessments are shown in Table III. Patient reported QOL mean total scores were lowest during week 2 of induction therapy. However, the QOL assessment of patient and parent proxy reported mean total scores significantly improved over time (P = 0.0001). At initiation of interferon therapy, the PedsQL v.4.0 mean total scores were lower, possibly due to the preceding surgical procedures (WLE and SLNB +/- CLND), than the healthy normative means.[25] However, the scores improved to levels equal to or above normative means at 6 and 12 months off therapy. By parent report, few behavioral problems were noted, as scores on the Behavioral Symptoms Index of the BASC-2 were within normative levels at baseline, and did not change over time. Parental

report of child executive functions on the BRIEF was within the average range at baseline, and showed significant improvement over time ($P < 0.05$).

Pharmacokinetics

IFN α -2b pharmacokinetic studies were performed in 16 patients (109 samples, ~7 samples/patient). The median (range) systemic clearance (CL), volume of central compartment (V_c), α half-life and β half-life were 15.3 L/hr/m² (7.5–29.1 L/hr/m²), 25.1 L/m² (13.9–49.2 L/m²), 0.7 hours (0.4–1.4 hours) and 14.7 hours (12.5–28.2 hours), respectively. The median (range) AUC_{0-∞} was 5,026 pcg*hr/mL (2,642–10,270 pcg*hr/mL). A representative concentration-time profile for IFN α -2b is depicted in Figure 1A.

Serial pegylated IFN α -2b pharmacokinetic studies were performed on a total of 9 patients. The median (range) AUC_{0-∞} was 50,556 pcg*hr/mL (36,166–58,980 pcg*hr/mL) after the first dose (week 5; 7 patients) and 48,480 pcg*hr/mL (34,024–59,857 pcg*hr/mL) at steady state (week 28; 6 patients). The median (range) apparent CL and V_c , and half-life were 19.8 mL/hr/kg (16.7–31.4 mL/hr/kg), 772 mL/kg (594–1410 mL/kg), and 24.8 hours (16.6–40.6 hours), respectively. Based on 63 samples from 17 patients (median of 4 per patient) the median (range) steady-state trough concentrations for pegylated IFN α -2b was 52.8 pcg/mL (13.8–152.4 pcg/mL). A representative pegylated IFN α -2b concentration-time profile is shown in Figure 1B.

DISCUSSION

This is the first prospective study to incorporate pegylated IFN α -2b during maintenance therapy in children and adolescents with malignant melanoma. Our results demonstrate that this therapy is feasible and safe in this patient population.

The use of pegylated IFN α -2b based on the EORTC 18991 in adult patients with resected stage III melanoma that led to the approval of the pegylated IFN α -2b for this indication consisted of an induction phase of 6 mcg/kg/dose SQ weekly for 8 weeks followed by a planned maintenance phase of 3 mcg/kg/dose for 5 years.[16, 17] Although there was an improvement in DFS in patients who were randomized to receive pegylated IFN α -2b, 37% of patients discontinued therapy for toxicity (25% due to fatigue) and the median treatment duration was only 12 months (range, 3.8–33.4). In contrast to this adult study and with the caveat that we employed a lower dose of pegylated IFN α -2b, discontinuation of therapy was observed in only 3 (13%) of 23 participants in our study and whereas the most common grade 3 or 4 toxicity was fatigue (16%) and liver function abnormalities (11%) in EORTC 18991,[16] the most common toxicities during pegylated IFN α -2b therapy in our study were neutropenia (35%) and liver function abnormalities (17%). This finding is consistent with our previous study of non-pegylated interferon where grade 3 or 4 neutropenia was also more common in children than constitutional symptoms as observed in adults.[9]

Adult patients undergoing interferon therapy for melanoma not only report an intolerable level of fatigue, but an overall global decrease in quality of life as well as depressive and cognitive difficulties.[26-28] In order to better understand the impact of interferon on QOL and psychological function in pediatric patients with melanoma, we used validated measures

to systematically assess these symptoms in our study. Despite a significant percentage of patients coded with grade 1 or 2 fatigue (induction 70%; maintenance 83%) and mood alteration (induction 17%; maintenance 39%) by CTCAE v3.0, our results using the validated measures for QOL and psychological functioning, demonstrated improvement in QOL over the course of therapy and following completion of therapy as reported by the patient and parent proxy. Similarly, we found no decline in psychological functioning, which was within normal limits, and observed an improvement in executive functioning over the course of treatment. While it does not appear that there is an adverse impact of interferon therapy on QOL, depression or executive function, our sample size was small and therefore for each individual patient it is imperative for physicians to assess for mood alterations and symptoms that may impact QOL. This may be challenging in young patients with pre-existing behavioral issues that may be exacerbated by the change in routine associated with the diagnosis and treatment of a malignancy.

Thyroid abnormalities have been reported in up to 50% of cases with interferon therapy[29], but have not been well characterized in the pediatric population. In our study, thyroid dysfunction developed in 35% of patients. The most commonly reported thyroid abnormality, both in the literature and in our study, was autoimmune thyroiditis. It was diagnosed most commonly during the maintenance phase of our study and resolved in only 2 patients during the study period. Autoimmune thyroiditis is caused by damage to the epithelial cells of the thyroid following immune system activation. Non-autoimmune thyroiditis due to direct damage by interferon has also been described and may have occurred in one of our patients with persistent hypothyroidism and negative thyroid autoantibodies.[29] Primary hypothyroidism required treatment in all of our patients who to date continue to require replacement therapy.

The induction of serologic and clinical manifestations of autoimmunity with interferon in patients with melanoma is not restricted to thyroid-related autoantibodies. In a prospective study of adult patients with melanoma who were treated with high dose interferon therapy, 26% developed autoantibodies (anti-thyroid, ANA, anti-DNA and ACA antibodies) or clinical manifestations of autoimmunity and this feature was an independent prognostic factor for improved DFS and OS in that study.[30] In a retrospective study evaluating 3 autoantibodies (ANA, ACA and TGB antibodies) in patients receiving intermediate dose interferon in two clinical trials, seroconversion was not associated with improved outcome. [31] Similar findings were noted in patients receiving pegylated interferon in EORTC 18991. [32] In our study, we performed serologic testing for 5 autoantibodies and found seroconversion in 10 (43%) of 23 patients during therapy. Because of the small number of participants and excellent outcomes in our study, we are unable to comment on whether seroconversion is a prognostic factor for DFS. It is also unclear if there are any clinical implications for those few patients with persistently positive titers.

We evaluated the single-dose disposition of IFN α -2b, and both the single-dose and multiple-dose pharmacokinetics of pegylated IFN α -2b. The median IFN α -2b AUC_{0- ∞} and systemic clearance and pegylated IFN α -2b apparent clearance in our study were in agreement with previous studies in adults after accounting for differences in dosage.[12, 33-35]

Based on prior reports investigating the pharmacokinetics of pegylated IFN α -2b and IFN α -2b in patients with chronic hepatitis C (Merck; data on file), we substituted a subcutaneous dosage of 1 μ g/kg/week pegylated IFN α -2b to achieve similar exposures to IFN α -2b 30 million units/week subcutaneously.[14] We found that the median pegylated IFN α -2b exposure was greater than the cumulative weekly exposure reported for IFN α -2b given TIW, suggesting that our patients had a greater exposure than predicted. However, this result should be interpreted with caution because of differences in analytical techniques, bioactive forms of interferon, and patient populations.

The use of adjuvant high dose interferon in adult and pediatric patients with high-risk melanoma is controversial. Those who dispute the use of adjuvant interferon cite modest benefit at the expense of cost and toxicity as arguments against its use. There are additional considerations related to using interferon in the adjuvant setting for the pediatric population. First, in pediatrics, the benefit in OS and DFS versus observation alone is unknown. The low incidence of the disease in this population precludes a large and/or randomized study mimicking those performed in adults to answer this question. The second issue is the diagnostic dilemma of atypical spitzoid tumors (AST) commonly encountered in children. ASTs often have some morphologic features that would suggest that the lesion could be malignant and are frequently associated with a positive sentinel node. However, ASTs rarely metastasize and therefore do not carry the same prognostic significance, particularly in prepubertal children, as conventional melanoma and may not require adjuvant therapy. Nonetheless, because there are small subsets of children with ASTs who develop metastatic disease,[36] we included patients with biologically indeterminate spitzoid neoplasms in our study. Molecular profiling of ASTs will help better define the need for adjuvant therapies in these patients.[37]

Recent approval of immune checkpoint inhibitors (e.g., ipilimumab and nivolumab) and small molecules targeting mutations in BRAF (e.g., vemurafenib) and downstream inhibition of MEK (e.g., trametinib) have led to trials evaluating these agents in the adjuvant setting for high risk patients. The first of the results of these trials was recently published and showed that ipilimumab after complete resection of stage III melanoma improved DFS compared to observation alone.[38] However, ipilimumab-related toxicities were significant. Further, it is important to recognize that the early trials in patients with metastatic disease with both checkpoint inhibitors and those targeting BRAF only benefit a subset of patients. The tumor in ~50% percent of patients with melanoma does not harbor a BRAF mutation.[39-41] Further, the development of resistance to these inhibitors is a common problem.[42] Because of the challenges with these new therapies, adjuvant interferon for high-risk patients deserves consideration. In our study, we show that in children with high-risk melanoma, the convenient weekly SQ pegylated IFN α -2b is feasible as maintenance therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACA	anticardiolipin antibody
AJCC	American Joint Committee on Cancer
ANA	anti-nuclear antibody
AST	atypical spitzoid tumor
AUC	area under the curve
BASC-2	Behavioral Assessment System for Children, 2nd Edition
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BRIEF	Behavioral Rating Inventory of Executive Function
BUN	blood urea nitrogen
CL	systemic clearance
CLND	complete lymph node dissection
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free interval
DNA	deoxyribonucleic acid
EFS	event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
IFN α-2b	interferon
MEK	mitogen-activated protein kinase/extracellular signal-regulated kinase
OS	overall survival
PedsQL	Pediatric Quality of Life Inventory
PEG	polyethylene glycol
QOL	quality of life
SLNB	sentinel lymph node biopsy
SQ	subcutaneously
TGB	thyroglobulin
TIW	three times per week
TPO	thyroid peroxidase

V_c	volume of central compartment
WLE	wide local excision

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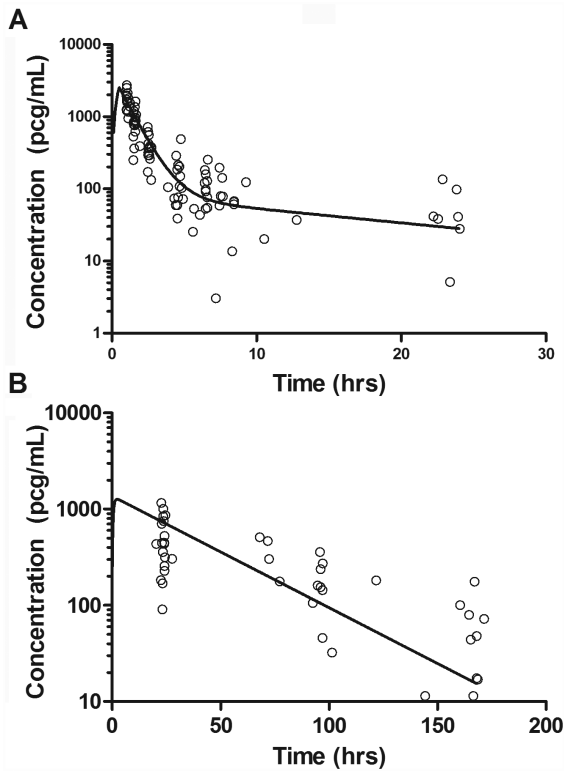


Figure 1. Population concentration-time profile of interferon α -2b (A) and pegylated interferon α -2b (B) superimposed with observed (o) concentrations.

TABLE I

Patient Demographics and Clinicopathologic Characteristics (N = 23)

Age (years)		No. of Patients (%)
	Median (range)	10 (2–20)
Sex		
	Female	15
	Male	8
Race		
	White	17
	Black	2
	Other	3
	Unknown	1
Primary Tumor Site		
	Extremity	10
	Trunk	8
	Head and Neck	6
Histology		
	Spitzoid ^a	10
	Nodular	5
	Superficial spreading	5
	Other ^b	3
Breslow Thickness (mm) (n=15)		
	Median (range)	3.4 (1.2-7.8)
No. of involved lymph nodes		
	Median (range)	1 (0-3)
Ulceration		
	Present	10
	Absent	13
Stage^c		
	IIC	2
	IIIA	11
	IIIB	10

^aSpitzoid neoplasms, biologically indeterminate;^bEpithelioid (1), spindle cell (1), indeterminate (1);^c2002 American Joint Committee on Cancer (AJCC) Staging System

TABLE II

Grade 3 or 4 Treatment-Related Toxicity during Induction and Maintenance Therapy (N= 23)

Adverse Events ^a		Induction	Maintenance
		Grade 3 or 4 No. (%)	Grade 3 or 4 No. (%)
Hematologic			
	Neutropenia	19 (83)	8 (35)
	Leukopenia	2 (9)	2 (9)
Non-hematologic			
Metabolic/Laboratory			
	Elevated ALT	4 (17)	4 (17)
	Elevated AST	2 (9)	2 (9)
	Hypertriglyceridemia	1 (4)	-
	Elevated amylase	-	1 (4)
Constitutional			
	Fever (absence of neutropenia)	1 (4)	-
Gastrointestinal			
	Cholecystitis	-	1(4)
Musculoskeletal			
	Joint effusion	-	1 (4)
	Joint Function	-	1 (4)
Neurology			
	Mood alteration	-	1 (4)
Pain			
	Headache	1 (4)	2 (9)

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase

^aGrades according to National Cancer Institute Common Terminology Criteria for Adverse Events (Version 3.0). Each adverse event was counted once (highest grade) for each patient during induction and also once for each patient during maintenance

TABLE III

Mean total scores (standard deviation) for each of the quality of life (PedsQL 4.0 and PedsQL3.0) measures and T-scores for each of the psychologic (BASC-2 and BRIEF) measures prior to, during and at the completion of therapy.

Time point	PedsQL 4.0 Total, Child ^{a, b}	PedsQL 4.0 Total, Parent ^{a, c}	PedsQL 3.0 Cancer Total ^a , Child	PedsQL 3.0 Cancer Total ^a , Parent	BASC-2 BSI ^d , Parent	BRIEF GEC ^e , Parent
Pre-Therapy	75.5 (18.4)	70.3 (19.1)	--	--	44.9 (8.1)	47.9 (12.8)
Week-2	71.6 (18.7)	71.8 (16.4)	71.1 (17.2)	73.2 (13.9)	--	--
Week-4	77.2 (16.3)	74.4 (17.9)	76.1 (15.4)	75.1 (15.2)	45.9 (8.3)	50.8 (11.9)
Week-8	79.3 (17.4)	79.1 (16.6)	79.2 (19.2)	81.4 (11.6)	--	--
Week-12	77.8 (20.6)	79.0 (19.0)	78.5 (14.7)	78.7 (17.7)	--	--
Week-24	80.6 (15.6)	82.2 (14.5)	77.1 (16.0)	81.6 (17.1)	44.2 (6.9)	48.6 (12.4)
End of Therapy	80.4 (16.1)	87.5 (15.3)	77.0 (16.5)	85.6 (13.8)	47.2 (11.1)	47.6 (12.6)
6-months Post	87.5 (12.5)	86.0 (17.6)	83.7 (18.0)	85.0 (11.5)	42.3 (7.2)	42.6 (8.1)
12-months Post	91.0 (7.1)	87.3 (17.5)	85.4 (8.9)	89.1 (11.6)	--	--

Abbreviations: BASC-2, Behavior Assessment System for Children-Second Edition; GEC, Global Executive Composite; BSI, Behavior System Index; BRIEF, Behavior Rating Inventory of Executive Function.

^aHigher scores reflect better quality of life;

^bHealthy sample normative means for child report is 83.0 (14.8);

^cHealthy sample normative means by parent report is 87.6 (12.3);

^dHigher scores reflect greater behavioral problems;

^eHigher scores reflect poorer executive functions.